AN OPEN-LABEL, DOSE-FINDING AND PROOF OF CONCEPT STUDY OF THE PD-L1 PROBODY™ THERAPEUTIC, CX-072, AS MONOTHERAPY AND IN COMBINATION WITH YERVOY® (IPILIMUMAB) OR WITH ZELBORAF® (VEMURAFENIB) IN SUBJECTS WITH ADVANCED OR RECURRENT SOLID TUMORS OR LYMPHOMAS

PROTOCOL MODULE NUMBER: CTMX-M-072-001

(PROCLAIM-001: PROBODY CLINICAL ASSESSMENT IN MAN CX-072 CLINICAL TRIAL 001)

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Sponsor:	CytomX Therapeutics, Inc. 151 Oyster Point Boulevard Suite 400 South San Francisco, CA 94080-1913 Telephone: +1-650-515-3185 Fax: +1-650-351-0353
Medical Monitor:	[redacted] Medical Director, Clinical Development CytomX Therapeutics, Inc. 151 Oyster Point Boulevard Suite 400 South San Francisco, CA 94080-1913 Telephone: +1-650-825-5321 Mobile: +1-415-680-8258 Fax: +1-650-351-0353
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1. SIGNATURE PAGE

Title of Protocol Module:

An Open-Label, Dose-Finding and Proof of Concept Study of the PD-L1 Probody™ Therapeutic[1], CX-072, as Monotherapy and in Combination with Yervoy® (Ipilimumab) or With Zelboraf® (Vemurafenib) in Subjects with Advanced or Recurrent Solid Tumors or Lymphomas

Protocol Module No: CTMX-M-072-001
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1.1. Sponsor Approval

[redacted]
Signing Reason: I approve this document
Signing Time: 20-Aug-2020 | 11:44 PDT
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20-Aug-2020 | 11:44 PDT

_____ _____

[redacted] Date
Senior Vice President, Chief Medical Officer, CytomX Therapeutics, Inc.

1.2. Investigator Agreement

By signing this page, I attest that I have read and understand the contents of Common Core Document CTMX-C-001 (APPENDIX 1), Protocol Module CTMX-M-072-001, and any subsequent amendments to both documents. I agree to adhere to the design, conduct, and reporting requirements of the Protocol Module as stated in the Common Core Document and the CX-072 specific Protocol Module, CTMX-M-072-001, to my obligations to the Sponsor as described in the Common Core Document and executed contracts between myself, my Institution, and CytomX Therapeutics, Inc., the Sponsor.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date (dd/mmm/yyyy): _____

[1] "PROBODY, IHZ, and QZ are trademarks of CytomX Therapeutics, Inc. All other brands and trademarks referenced herein are the property of their respective owners."

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
5-FU	5-fluorouracil
^{89}Zr	zirconium-89
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRCA	breast cancer gene
bTMB	tumor mutational burden in blood
CAR	chimeric antigen receptor
CEA	carcinoembryonic antigen
CI	confidence interval
C_{max}	peak plasma concentration
C_{min}	minimum plasma concentration
CR	complete response
cSCC	cutaneous squamous cell carcinoma
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CYP	cytochrome P450
DLT	dose limiting toxicity
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
EOI	end of infusion
ER	estrogen receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FIH	first-in-human
GI	gastrointestinal
GLP	Good Laboratory Practices
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
hTMB	high tumor mutational burden
ICF	informed consent form
IHC	immunohistochemistry
IP	investigational product
irAE	immune-related adverse event
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRF	independent review facility
IRR	infusion-related reaction
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	intravenous
IWRS	interactive web response system
K_d	elimination rate constant
mAb	monoclonal antibody(ies)
MABEL	minimum anticipated biological effect level
MAD	maximum achieved dose
Mb	megabase
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MEK	mitogen-activated protein kinase

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	non-human primate
NOAEL	no-observable-adverse-effect level
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PD	pharmacodynamic(s)
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	oral
popPK	population pharmacokinetic
PR	partial response
QSP	quantitative systems pharmacology
qXh	every X hours
qXwk	every X weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SCC	squamous cell carcinoma
SD	stable disease
SOC	standard of care
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
$t_{1/2}$	terminal half-life
TET	thymic epithelial tumor
TMDD	target mediated drug disposition
TME	tumor microenvironment
TNBC	triple negative breast cancer
TPS	tumor proportion score
TTR	time to response
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma
US	United States
USP	United States Pharmacopeia

4. INTRODUCTION

4.1. PD-1 and PD-L1 Inhibitors

The immune system has recently emerged as a highly promising target for the treatment of cancer. T-cells are capable of recognizing many cancers as foreign, and, when optimally mobilized, can induce potent and durable responses in patients against many cancer types. However, tumors can evade immunity by exploiting the same mechanisms that in healthy tissue serve to regulate immune function. One such mechanism is through expression of programmed cell death ligand 1 (PD-L1), a ligand that negatively regulates T-cell activity through its interaction with programmed cell death 1 (PD-1), an inhibitory receptor expressed on activated T-cells. The normal role of PD-L1 is to minimize immune-mediated damage to tissues under conditions of chronic T-cell stimulation or from attack by autoreactive T-cells. Expression of PD-L1 is dynamic and induced most potently by interferon gamma produced by activated T-cells, and it functions in a negative feedback loop to suppress the activity of T-cells involved in a local tissue attack. PD-L1 is now understood to be a dominant means by which tumors can evade the immune system. Clinical trials have confirmed the capacity of PD-1/PD-L1 blockade to effectively restore the activity of tumor specific immunity, leading to responses in approximately 60% of patients with advanced melanoma and approximately 20% of patients across multiple additional tumor types (Herbst 2014; Lipson 2015). For example, nivolumab (Opdivo®, Bristol-Myers Squibb Company) has been approved for the treatment of metastatic squamous non-small cell lung cancer and classical Hodgkin Lymphoma; nivolumab and pembrolizumab (Keytruda®, Merck Sharp and Dohme Corporation) have both been approved for the treatment of advanced melanoma; atezolizumab (Tecentriq®, Genentech, Inc.), durvalumab (Imfinzi®, AstraZeneca Pharmaceuticals LP), and avelumab (Bavencio®, EMD Serono, Inc.) have been approved for locally advanced or metastatic urothelial carcinoma; cemiplimab-rwlc (Libtayo®, Regeneron Pharmaceuticals, Inc.) has been approved for cutaneous squamous cell carcinoma (cSCC); and avelumab has been approved for metastatic Merkel cell carcinoma (MCC). These and other new agents will likely receive approval, as monotherapy and/or in combination with other agents, for the treatment of other tumors as well.

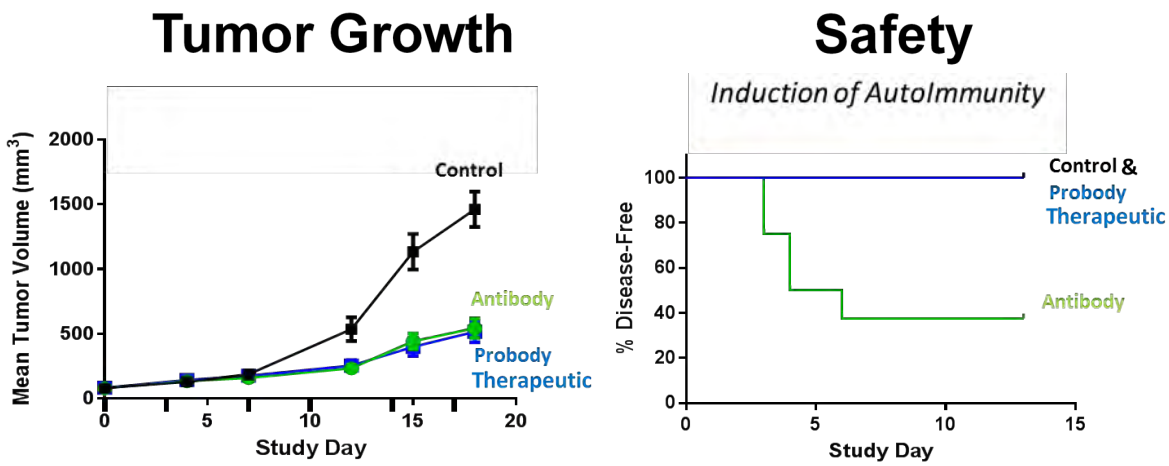
4.2. CX-072 Overview

CX-072 is a Probody® therapeutic directed against PD-L1 for the treatment of cancer and is the first under the CytomX Probody platform to be studied in humans. Probody therapeutics are fully recombinant monoclonal antibody (mAb) prodrugs designed to be preferentially activated by proteases associated with the tumor microenvironment (TME). They differ from unmodified mAb by the recombinant addition of a cleavable Prodomain comprised of a mask and protease-cleavable substrate, which blocks the antibody. This mask is designed to block binding to its target antigen until the Prodomain can be removed by tumor-associated protease cleavage at the substrate and released in the presence of tumor-associated proteases. As such, Probody therapeutics are administered in a form designed to bind their target in tumor tissue but not in normal circulating cells or healthy tissues. In nonclinical models, Probody therapeutics, including those targeting PD-L1, have been shown to reduce toxicity of the relevant unmasked parent antibody while maintaining its antitumor activity. In patients, Probody therapeutics may be particularly useful in clinical settings where target binding in healthy tissue limits patient access to potent, efficacious regimens. CX-072 is designed to widen the therapeutic window by

reducing interaction with PD-L1 in normal tissue environments while maintaining interaction with tumor tissue.

CX-072 is a Probody therapeutic derived from a proprietary human anti–PD-L1 mAb. In patients with various cancers, conventional anti–PD-L1 mAb (atezolizumab, avelumab, and durvalumab) and anti–PD-1 mAb (nivolumab and pembrolizumab) have demonstrated clinical effectiveness as monotherapy and/or in combination with other immunotherapies. However, significant life-threatening toxicities have been observed with these agents, particularly in combination regimens. The most common serious adverse events (SAEs) that lead to premature discontinuation of therapy or death are immune-related and are most likely attributable to drug-induced inflammation outside of the tumor (Larkin 2015). CX-072 is intended to provide antitumor efficacy similar to that of other PD-L1 and PD-1 inhibitors, but with an improved safety profile, especially when given in combination with other therapeutics, such as ipilimumab or vemurafenib.

Figure 1: PD-L1 Probody Therapeutic



PD-L1 = programmed cell death ligand 1.

Expression, purification, formulation, characterization, stability, and administration of CX-072 are similar to that of other mAb.

CX-072 is designed to be activated by a number of proteases associated with the TME, including serine proteases and matrix metalloproteinases classes. These proteases were chosen to activate CX-072 because there is published evidence that they are associated with human tumors (LeBeau 2013; Overall 2006), and generally, they have low activity in blood or in select normal tissues.

A variety of in vitro, ex vivo, and in vivo experiments have been performed to demonstrate that Probody therapeutics are effectively activated by tumor-associated proteases. These experiments were performed with either CX-072 or other Probody therapeutics that are representative of what would be expected of CX-072 because their substrate sequences are similar.

Data from these experiments have demonstrated that these Probody therapeutics are efficacious in multiple tumor models, including human cell line xenografts, patient-derived xenografts, mouse genetic models, and mouse syngeneic tumor models. These data demonstrate that Probody therapeutics are active under a wide variety of tumor conditions in vivo. In contrast,

Probody therapeutic activation and target binding in circulation and normal tissues is limited, as demonstrated by nonclinical ex vivo and in vivo models.

CytomX developed a technique used to screen human tissues directly for the presence of protease activity ex vivo. Frozen human tissue samples were incubated with labeled Probody therapeutic, and cleavage and activation of the Probody therapeutic were detected either by binding of the Probody therapeutic to its target in the tissue sample (IHZ™ assay) or by assaying the Probody therapeutic directly for cleavage and removal of the mask using quantitative capillary electrophoresis (QZ™ assay). Utilizing the IHZ assay, CytomX analyzed approximately 200 human tumors taken from many different tumor types, and > 90% of samples had sufficient protease activity under these assay conditions to activate a Probody therapeutic that can be cleaved by proteases that also activate CX-072. This reflects the design of the Probody substrate to be cleavable by at least 1 of several different tumor-associated proteases. Accordingly, patient selection based on protease activity in tumors likely will not be necessary in the proposed studies, although CytomX intends to collect data on protease activity in patient samples.

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- [redacted]

4.4.2. Dose Escalation

First, this study will evaluate the safety of CX-072 as monotherapy (Part A), and will initially enroll 1 patient per cohort, at doses of 0.03, 0.1, and 0.3 mg/kg, until ≥ Grade 2 treatment-related adverse events (AEs) are observed or the 1.0 mg/kg dosing cohort opens for enrollment, whichever comes first. Thereafter, an additional 2 patients will be enrolled at that dose level. All subsequent dose levels will enroll in the conventional 3 + 3 design. The maximum tolerated dose (MTD) is defined as the highest dose tested at which no more than 1 of 6 patients has experienced a dose limiting toxicity (DLT). This recommendation is based on the following:

- The safety of the approved PD-L1 inhibitor, atezolizumab, as well as other PD-L1 inhibitors in development have not shown acute toxicities in Phase 1 dose-escalation studies;
- [redacted]
- Early signs of clinical activity were not demonstrated at doses below 1 mg/kg for agents in this class (PD-1 and PD-L1 inhibitors, including BMS-936559 [PD-L1 inhibitor] [Brahmer 2012], atezolizumab [Herbst 2014], MEDI4736, and avelumab [Powles 2014; Segal 2015; Spigel 2015]).

The initial exploration of monotherapy will use 1-patient cohorts in the first 3 dose levels to limit the number of cancer patients treated with sub-therapeutic doses. Once the initial assessment is complete in these patients and higher dose levels have passed the DLT dose assessment, intra-patient dose escalation will be permitted to potentially more therapeutic dose levels, but only for patients in these very first dose levels (0.03, 0.1, and 0.3 mg/kg).

4.4.3. CX-072 Monotherapy Dose Effect

Once a given dose level in Part A has been cleared (e.g., the dose has been declared safe and enrollment into the next dose level has been initiated), 6 patients each with PD-L1+ cancer (at least 2 patients in each cohort with thymic epithelial tumor [TET]) will be enrolled into the CX-072 monotherapy dose effect part of the study (Part A2) at that dose.

The primary objective of Part A2 is to refine the selection of the MTD/maximum achieved dose (MAD) by exploring the relationship between dose/exposure versus the levels of activated CX-072 in the TME and in plasma in patients with PD-L1+ tumors. This analysis is an important measure of CX-072 performance (which may vary by dose). The relationship between dose/exposure versus safety and efficacy of CX-072 will also be evaluated in Part A2.

To generate additional PK and CX-072 cleavage data for dose selection, an additional 6 patients will be enrolled to each of 4 dose levels (0.3, 1, 3, and 10 mg/kg) in Part A2. Data from Part A2 will help refine the selection of the MTD/MAD by measuring the amount of cleaved, activated CX-072 in the TME and in the periphery using paired tumor and blood samples (as a proxy for healthy tissue in the periphery).

Data presented at American Society of Clinical Oncology (ASCO) 2017 reinforces that there is particularly high toxicity of PD-1/PD-L1 inhibitors in TET (Cho 2017; Giaccone 2017). Therefore, there is potential utility in gathering extra safety data at various doses in TET in the event that emerging clinical data support further evaluation in TET in the future.

The focus of Part A2 is to obtain a gauge of the relationship between CX-072 dose/exposure and efficacy and PD markers in patients with PD-L1+ cancer.

[redacted]

In Part A2, cohorts will be enrolled consecutively and, as such, each dosing cohort in Part A2 must be filled before the next cohort can open.

Patients must agree to participate in biomarker analysis and have a tumor site that is safe to biopsy.

4.5. Rationale for Combination Therapy

Nonclinical mouse studies conducted by CytomX have demonstrated the ability of a surrogate PD-L1 Probody therapeutic to provide comparable anti-tumor activity to that of its parental antibody, at comparable doses, while minimizing induction of systemic autoimmunity in a diabetes susceptible non-obese diabetic mouse model. CytomX has also demonstrated reduced occupancy of the PD-L1 Probody therapeutic on peripheral blood T-cells in tumor-bearing mice, consistent with its ability to protect against autoimmunity. In non-GLP pilot toxicology studies in both cynomolgus monkeys and rats, CX-072 has been well tolerated. By localizing its activity to

the TME, CX-072 is expected to reduce systemic toxicities and expand clinical opportunities for targeting the PD-1/PD-L1 pathway in combination therapies. For example, replacing nivolumab with an anti–PD-L1 Probody therapeutic may not only improve the safety of the combination with ipilimumab, but may also increase efficacy by permitting full doses of both agents.

Anti–PD-1/PD-L1 antibodies combined with the CTLA-4 inhibitor, Yervoy® (ipilimumab): efficacy gains at the expense of increased toxicity

Despite the enormous potential of PD-1/PD-L1 blockade and other immunotherapies, they are not effective in all patients. Consequently, combination therapy has been sought as a means to improve efficacy. When nivolumab, an anti–PD-1 antibody, is added to ipilimumab, an anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody, in patients with advanced melanoma, both efficacy and toxicity increase. Fifty-eight percent of the patients achieve objective responses with the combination, compared to 19% and 41% for monotherapy ipilimumab and nivolumab, respectively (Larkin 2015), but 55% of the patients experience drug-related Grade 3 to 4 AEs compared to 16% and 27%, respectively. Presumably, as these agents are administered systemically and both the PD-L1 and CTLA-4 proteins are present on normal tissue, the synergy of effect between the 2 agents is not confined to the tumor and inflammation in normal tissues results in meaningful, sometimes life-threatening toxicity.

One way to address the safety challenges with these combinations is by adjusting dose and schedule. However, to date this has proven insufficient to improve safety in a meaningful way. The combination of ipilimumab and nivolumab in advanced lung cancer, for example, is too toxic to be administered at full doses. When the doses are reduced by 1/3 and ipilimumab is administered less frequently (i.e., the “optimal” dose and schedule), approximately 30% of patients still experience treatment-related Grade 3 to 4 toxicities (Rizvi 2015). Most recently, Johnson reported 2 fatal cases of myocarditis with electrical instability and selective clonal T-cell infiltration in the myocardium and skeletal muscle (Johnson 2016). Therefore, new approaches are needed to reduce serious toxicities that occur with potent immunotherapy combinations, such as PD-1 pathway inhibitors combined with CTLA-4 inhibitors.

After the 1 mg/kg CX-072 monotherapy cohort in Part A has completed DLT evaluation and has been determined to be safe, as per protocol, evaluation of the safety of the combination of CX-072 with ipilimumab will be initiated in Part B1 and Part B2.

Part B1 of the study will evaluate a concomitant schedule of the combination of CX-072 and ipilimumab in patients with advanced solid tumors or lymphoma who have exhausted standard of care (SOC) therapies. Eligible patients cannot have had prior immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitors, but are excluded if there is any immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated. Patients enrolled into Part B1 will receive escalating doses of CX-072 administered concomitantly with 3 mg/kg ipilimumab. If 10 mg/kg of CX-072 plus 3 mg/kg of ipilimumab is judged safe (as per protocol and confirmed by the Safety Review Committee [SRC]), the dose of ipilimumab with 10 mg/kg of CX-072 will be escalated to 6 mg/kg ipilimumab. See Section 14.3 for details regarding biopsies associated with this cohort.

Part B2 of the study will also evaluate a concomitant schedule of the combination of CX-072 and ipilimumab in patients with advanced solid tumors or lymphomas who have exhausted SOC therapies. However, unlike Part B1 where patients must be PD-1/PD-L1 inhibitor naive,

patients enrolled into Part B2 must have received a prior PD-1/PD-L1 inhibitor provided that the PD-1/PD-L1 inhibitor was discontinued for reasons other than toxicity.

As patients in this part will most likely have progressed on or post PD-1/PD-L1 inhibitor treatment, the starting dose for Part B2 is 3 mg/kg CX-072 for the combination with 3 mg/kg ipilimumab, followed by escalation to 6 mg/kg. This way, lower doses of CX-072 will be spared from this patient population and increase the potential for clinical benefit. If no MTD for the combination with 3 mg/kg ipilimumab is established, the 10 mg/kg dose level of CX-072 will be evaluated in combination with 6 mg/kg ipilimumab. See Section 14.3 for details regarding biopsies associated with this cohort.

Anti–PD-1/PD-L1 antibodies with the kinase inhibitor, vemurafenib

Additional combinations of PD-1/PD-L1 inhibitors are also limited by significant toxicity. These include the combination of vemurafenib and the PD-L1 inhibitor, atezolizumab. Severe skin and neurological toxicities were reported in 2 patients with advanced melanoma who received a PD-1 inhibitor followed by vemurafenib (Johnson 2013). The toxicities were severe enough that vemurafenib treatment had to be discontinued in both cases.

Updated clinical data from a study in patients with previously untreated melanoma explored concomitant administration of atezolizumab with vemurafenib were reported at the Society for Melanoma Research 2015 International Congress (Hamid 2015). Initially, 3 patients were treated in cohort 1 (20 mg/kg q3wk of atezolizumab and 720 mg twice daily of vemurafenib). Grade 3 rashes and Grade 3 elevations in liver function tests were observed in the cohort. Two of the initial 3 patients responded, including 1 complete remission. To mitigate toxicity, the protocol was amended to initiate treatment with a run-in period with vemurafenib monotherapy twice daily for 56 days (n = 8) or 28 days (n = 6). Atezolizumab was then administered IV q3wk at 20 or 15 mg/kg or 1200 mg in a fixed dose. The vemurafenib was given in a reduced dose of 720 mg during the combination period. Seventeen patients were evaluable for response, with 3 complete responses (CRs) and 10 partial responses (PRs) reported. Overall response rate was 75% and 100% with 1 CR in each of the 56- and 28-day vemurafenib run-in cohorts, respectively. The run-in combination was shown to be well tolerated and there were no DLTs or treatment-related discontinuations of atezolizumab. Grade 3 AE rates for the concomitant regimen were higher (67%), than either of the 56- or 28-day regimens (38% and 33%, respectively). As the approved dose of vemurafenib was only tolerated in the single agent phase of the run-in but not in combination with atezolizumab, this dose escalation study evaluates the safety of the CX-072–vemurafenib combination at approved vemurafenib doses based on the anticipated tolerability of CX-072.

After the 3 mg/kg CX-072 monotherapy cohort in Part A has completed DLT evaluation and has been determined to be safe, as per protocol, evaluation of the safety of the combination of CX-072 with vemurafenib will be initiated in Part C of the current study. In Part C, escalating doses of CX-072, beginning at 1 mg/kg, will be administered to patients in combination with the approved dose of vemurafenib 960 mg administered in oral (PO) form twice daily in patients with B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E mutated, PD-1/PD-L1 and BRAF-inhibitor naive, advanced or metastatic melanoma. The selected doses for the combination will provide data on whether treatment with a targeted immunotherapy agent, CX-072, can mitigate the toxicity previously seen when combining vemurafenib with a

PD-L1 agent. There is no plan to add a mitogen-activated protein kinase (MEK) inhibitor to the vemurafenib/CX-072 combination at this time for the following reasons:

- Synergy between BRAF and PD-1 inhibitors has been demonstrated pre-clinically (Cooper 2014);
- Vemurafenib is approved as a single agent for the treatment of melanoma; and
- There are mixed data regarding the immunosuppressive effect of MEK in combination with vemurafenib/PD-L1.

Therefore, the safety of a 2-drug combination will be explored before adding a third agent.

4.6. Study Rationale

4.6.1. Study Rationale for Dose Escalation (Parts A Through C)

This is an FIH, Phase 1/2a, open-label, multicenter, dose escalation, multidose study designed to evaluate the safety and tolerability as well as determine the MTD or MAD of CX-072 as monotherapy and in combination with ipilimumab or vemurafenib. As discussed in Section 4.4.2, the first part of the study (Part A) is a dose escalation of CX-072 monotherapy starting at 0.03 mg/kg up to 30 mg/kg administered q2wk. The rationale for the starting dose of CX-072 monotherapy is discussed in Section 4.4.1. The rationale for the dose frequency is discussed in Section 4.4.5. Part A2 is designed to help refine the selection of the MTD/MAD by measuring the amount of cleaved, activated CX-072 in the TME and in the periphery using paired tumor and blood samples (as a proxy for healthy tissue in the periphery).

As discussed in Section 4.5, the combination of checkpoint inhibitors that block the PD-1 pathway (e.g., nivolumab) with anti-CTLA-4 (e.g., ipilimumab), demonstrate synergistic effects in efficacy and toxicities which can be dose limiting. CX-072 is designed to be preferentially activated in the TME. It is hypothesized that CX-072 may not only improve the safety of the combination with ipilimumab but may also increase efficacy by permitting full doses of both agents. Part B1 of the study is designed to evaluate the safety, tolerability, and MTD/MAD of CX-072 when combined with ipilimumab in immunotherapy naive patients. Part B2 is also designed to evaluate the safety, tolerability, and MTD/MAD of CX-072 when combined with ipilimumab; however, unlike patients in Part B1, patients in Part B2 will have received a prior PD-1/PD-L1 inhibitor (provided that the PD-1/PD-L1 inhibitor was discontinued for reasons other than toxicity).

Similar to the combination of nivolumab with ipilimumab, additional combinations of PD-1/PD-L1 inhibitors are also limited by significant toxicity, including the combination of vemurafenib and the PD-L1 inhibitor, atezolizumab (discussed in Section 4.5). Part C is designed to evaluate the safety, tolerability, and MTD/MAD of CX-072 in combination with vemurafenib in advanced or metastatic melanoma patients with BRAF V600E mutations. Patients in Part C will be PD-1/PD-L1 and BRAF-inhibitor naive. The selected doses for the combination will provide data on whether treatment with a targeted immunotherapy agent, CX-072, can mitigate the toxicity previously seen when combining vemurafenib with a PD-L1 agent.

4.6.2. Study Rationale for Dose Expansion (Parts D and E)

Enrollment in Parts A, A2, and B1 is complete and ongoing in Parts B2 and C. During dose escalation in Part A, the MTD was not reached; 46 patients in Parts A and A2 (including 10 patients with TET) received at least 1 dose of CX-072 monotherapy. The most recent presentation of these data was at the annual meeting of the European Society for Medical Oncology (ESMO) on 22 October 2018. Safety data showed 5 cases (11%) of Grade 3/4 CX-072-related AEs, 3 of which were immune-related: 1 case of pneumonitis in a patient with TET post-radiotherapy, 1 case of thrombocytopenia/neutropenia in a patient with TET, and 1 case of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increase in a subject with estrogen receptor (ER) positive breast cancer and liver metastasis.

Of all patients treated with at least 1 dose of CX-072 monotherapy at ≥ 3 mg/kg and who had at least 1 post-baseline tumor assessment (n=18), 3 patients had an objective response: 1 patient with TET receiving 3 mg/kg CX-072 (unconfirmed), 1 patient with triple negative breast cancer (TNBC) with skin lesions receiving 10 mg/kg CX-072 (PR confirmed), and 1 patient with endometrial carcinoma receiving 10 mg/kg CX-072 (unconfirmed). Additionally, 11 patients (61%) experienced stable disease.

Based on these encouraging findings, patients will be enrolled in Part D to further evaluate the safety, tolerability, and preliminary anti-tumor activity of CX-072 at 10 mg/kg.

Part D will enroll patients with specific tumor types that have failed to respond or showed tumor progression despite SOC therapy, or are not candidates for SOC therapy, or are unwilling to undergo SOC therapy, or for whom no available therapy is expected to convey clinical benefit. The tumor types selected for Part D are based on patients with unmet medical need that have had preliminary responses in this clinical trial (e.g., TNBC with skin lesions) or other published clinical trials as discussed in Section 6.7. Tumor types include undifferentiated pleomorphic sarcoma (UPS), small bowel adenocarcinoma, cSCC, MCC, TET, anal squamous cell carcinoma (SCC), TNBC with skin lesions, and high tumor mutational burden (hTMB).

5. STUDY OBJECTIVES

5.1. Primary Objectives

5.1.1. Primary Objectives for Parts A Through C

The primary objectives for Parts A through C of the study are:

1. Evaluate the safety and tolerability of multiple doses of CX-072, administered as monotherapy or in combination with ipilimumab or vemurafenib to patients with metastatic or locally advanced unresectable solid tumors or lymphomas; and
2. Determine the MTD and DLTs of:
   - CX-072 as a monotherapy administered to PD-1/PD-L1 naive patients,
   - CX-072 in combination with ipilimumab administered to PD-1/PD-L1 and CTLA-4 inhibitor naive patients,
   - CX-072 in combination with ipilimumab administered to patients that have had prior treatment with a PD-1/PD-L1 inhibitor, and
   - CX-072 in combination with vemurafenib administered to PD-1/PD-L1 naive patients.

5.1.2. Primary Objective for Parts D [redacted]

The primary objective of Parts D [redacted] of the study is to obtain preliminary and confirmatory evidence of the efficacy of CX-072 monotherapy, respectively, via the objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) (tumor types include: UPS, small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, TNBC with skin lesions, and hTMB [Part D only]), as assessed by Investigator (Part D) [redacted]

5.2. Secondary Objectives

5.2.1. Secondary Objectives for Parts A Through C

The secondary objectives for Parts A through C of the study are:

1. Obtain preliminary evidence of anti-cancer activity on the basis of the following endpoints in patients treated with CX-072 as monotherapy or when administered in combination with ipilimumab or vemurafenib:
   - ORR by RECIST v 1.1
   - ORR by modified immune-related response criteria as defined in the Common Core Document or Modified Cheson/Lugano Classification for Lymphomas
   - Time to response (TTR)
   - Duration of response (DOR)
   - Progression-free survival (PFS)
2. Characterize the incidence of ADA against CX-072 and ipilimumab

3. Characterize the single and multidose PK profile of CX-072 when administered alone, and CX-072, ipilimumab, and vemurafenib when administered in combination
4. Assess overall survival (OS) in patients receiving CX-072

5.2.2. Secondary Objectives for Parts D [redacted]

The secondary objectives for Parts D [redacted] of the study are:

1. Further characterize the efficacy of CX-072 monotherapy as evidenced by:
   - DOR as assessed by Investigator (Part D) [redacted]
   - [redacted]
   - ORR by modified immune-related (ir) RECIST as defined in the Common Core Document
   - PFS
2. Evaluate safety and tolerability of CX-072, administered as monotherapy
3. Characterize the incidence of ADAs against CX-072
4. Characterize the PK profile of CX-072
5. Assess OS in patients receiving CX-072

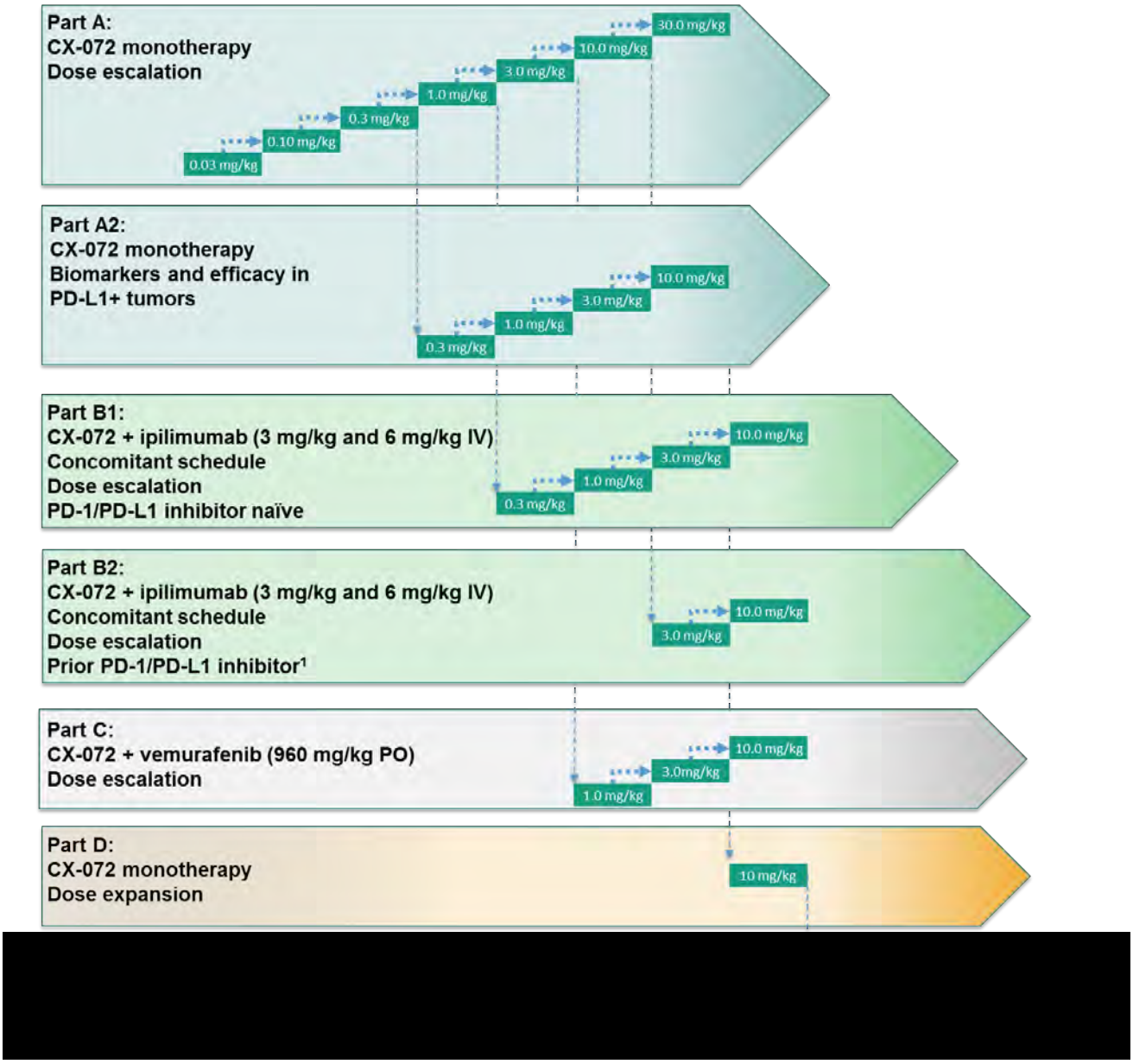
[redacted]

6. OVERVIEW OF STUDY DESIGN

This is an FIH, Phase 1/2a, open-label, multicenter, dose escalation, multidose study of CX-072. Approximately 60 study sites will be utilized. Parts A through C are designed to evaluate the safety and determine the MTD and/or MAD of CX-072 as monotherapy and in combination with ipilimumab or vemurafenib (see Figure 3). Parts D and E are designed to obtain preliminary and confirmatory evidence of anti-cancer activity, respectively. The doses to be tested in each part of the study and the dose escalation schema are outlined in Table 3 and Figure 4, respectively. Of note, this study will close without opening Part E. As of Amendment 09, Parts A-E are closed, and the long-term extension part of the study will begin (see Section 19).

All patients in Part A2 (CX-072 monotherapy), patients in Part B2 receiving CX-072 + 3 mg/kg ipilimumab (but not patients receiving 6 mg/kg ipilimumab), TNBC with skin lesions cohorts in Parts D and E will undergo pre- and on-study treatment tumor biopsies to explore potential predictive markers associated with CX-072 clinical activity.

Figure 3: Study Diagram



Note: In Part A, an expansion cohort of up to 22 additional patients is planned to be enrolled for an imaging substudy conducted in the Netherlands.
[1]Patients discontinued prior PD-1/PD-L1 for reasons other than toxicity.
IV = intravenous; PD-1 = programmed cell death; PD-L1 = programmed cell death ligand 1; PO = oral.

The study is divided into 7 parts:

- Part A: CX-072 monotherapy dose escalation and imaging substudy
  - Any metastatic or advanced unresectable solid tumor or lymphoma (n ≤ 33), measurable or nonmeasurable disease
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
  - CX-072 monotherapy (0.03, 0.1, 0.3, 1, 3, 10, and 30 mg/kg) IV every 14 days (q2wk)
  - Expansion cohort of up to 22 additional patients (10 mg/kg CX-072 monotherapy) for an imaging substudy conducted in the Netherlands
- Part A2: CX-072 monotherapy dose effect
  - Any metastatic or advanced unresectable solid tumor or lymphoma (at least 2 patients in each cohort with TET) (n ≤ 24), measurable disease, relapsed or refractory
  - Tumor proportion score (TPS) ≥ 1% membranous staining based on the DAKO PD-L1 Immunohistochemistry (IHC) 22C3 pharmDx
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
  - Participation in biomarker analysis and biopsies
  - CX-072 monotherapy (0.3, 1, 3, and 10 mg/kg) IV q2wk
  - Initiation of each cohort's enrollment requires successful completion of the Part A CX-072 monotherapy at that dose level
- Part B1: CX-072 plus ipilimumab combination dose escalation (PD-1/PD-L1 inhibitor naive)
  - Any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) (n ≤ 30), measurable or nonmeasurable disease
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
  - CX-072 (0.3, 1, 3, and 10 mg/kg) in combination with ipilimumab (3 or 6 mg/kg) IV q3wk × 4 doses in a concomitant schedule followed by CX-072 monotherapy IV q2wk
  - Initiation of cohort enrollment requires successful completion of the subsequent CX-072 monotherapy dose level tested in Part A

- Part B2: CX-072 plus ipilimumab combination dose escalation (prior PD-1/PD-L1 inhibitor)
  - Any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) ($n \leq 18$), measurable disease
  - Prior therapy with PD-1/PD-L1 inhibitors, discontinued for reasons other than toxicity
  - CTLA-4 inhibitor naive
  - CX-072 (3 and 10 mg/kg) in combination with ipilimumab (3 or 6 mg/kg) IV q3wk × 4 doses in a concomitant schedule followed by CX-072 monotherapy IV q2wk
  - Initiation of cohort enrollment requires successful completion of the subsequent CX-072 monotherapy dose level tested in Part A
  - Participation in biomarker analysis and biopsies (only in cohorts receiving CX-072 + 3 mg/kg ipilimumab [but not 6 mg/kg ipilimumab]) is mandatory
- Part C: CX-072 plus vemurafenib combination dose escalation
  - BRAF V600E mutation-positive metastatic or advanced unresectable melanoma ($n \leq 18$), measurable or nonmeasurable disease
  - BRAF-inhibitor naive
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy is not available to the patient)
  - CX-072 (1, 3, and 10 mg/kg) IV q2wk in combination with vemurafenib 960 mg PO twice daily (approximately every 12 hours [q12h]), concomitant schedule
  - Initiation of cohort enrollment requires successful completion of the subsequent CX-072 monotherapy dose level tested in Part A
- Part D: Expansion cohort for safety and efficacy at CX-072 10 mg/kg administered as monotherapy
  - Patients with metastatic or locally advanced unresectable tumor types of UPS ($n \leq 20$), small bowel adenocarcinoma ($n \leq 25$), cSCC ($n \leq 25$), MCC ($n \leq 25$), TET ($n \leq 25$), anal SCC ($n \leq 25$), TNBC with skin lesions ($n \leq 25$), and hTMB ($n \leq 25$) measurable disease, that have failed to respond or showed tumor progression despite SOC therapy, are not candidates for SOC therapy, are unwilling to undergo SOC therapy, or for whom no available therapy is expected to convey clinical benefit
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available to the patient)

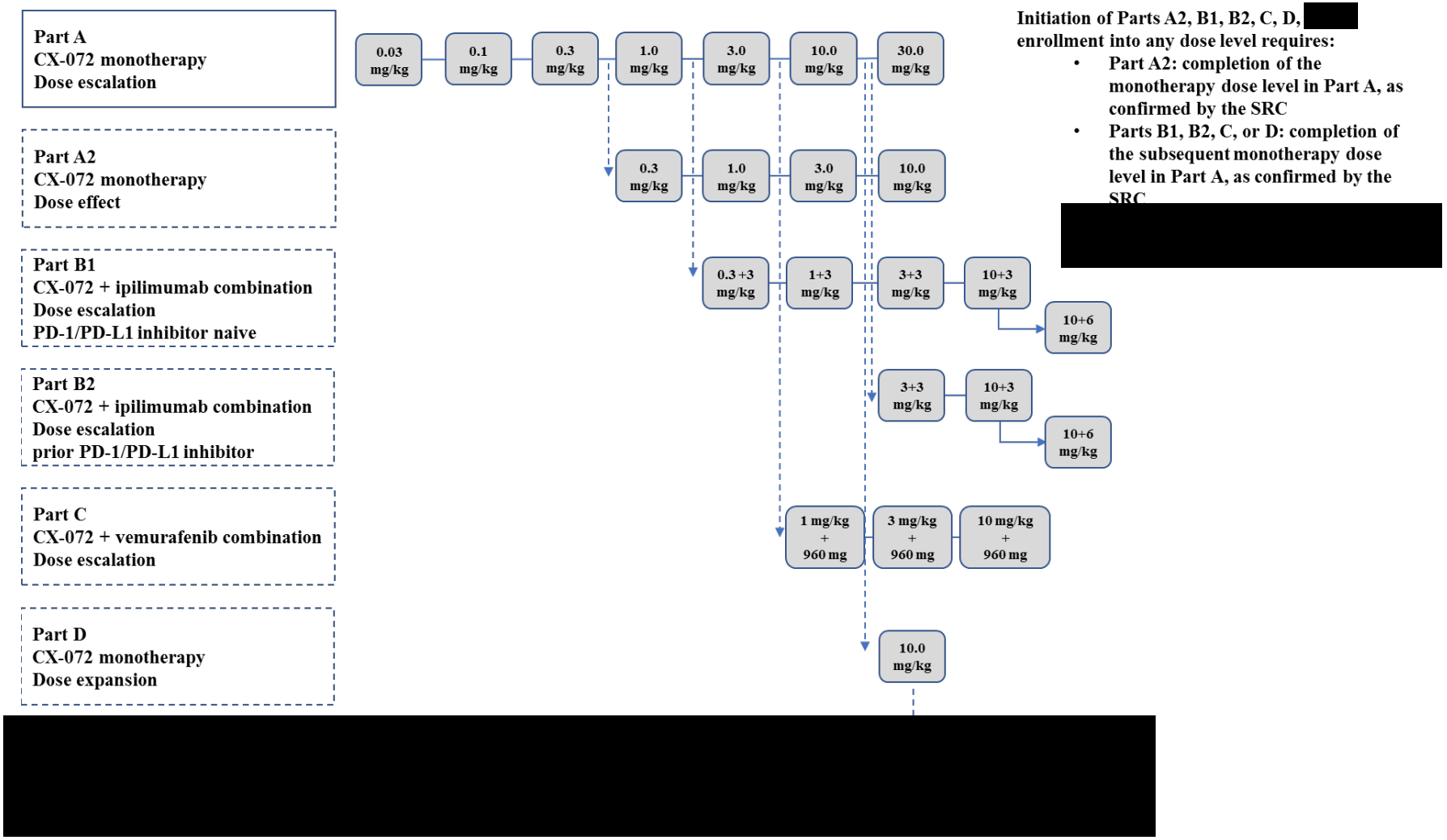
- [redacted]

Table 3: Doses to be Tested [1]

Dose CX-072 (mg/kg)	Cohort #	Part A Dose Escalation CX-072 (mg/kg) Monotherapy	Cohort #	Part A2 Dose Effect CX-072 (mg/kg) Monotherapy	Cohort #	Part B1 CX-072 + Ipilimumab Combination Dose Ipilimumab	Cohort #	Part B2 CX-072 + Ipilimumab Combination Dose Ipilimumab	Cohort #	Part C Dose Escalation CX-072 + Vemurafenib Combination Dose Vemurafenib PO q12h	Part D Dose Expansion
0.03	1A	0.03									10 mg/kg
0.1	2A	0.1									
0.3	3A	0.3	3A2	0.3	3B1	+ 3 mg/kg ipi					
1	4A	1	4A2	1	4B1	+ 3 mg/kg ipi			4C	+ 960 mg q12h vem	
3	5A	3	5A2	3	5B1	+ 3 mg/kg ipi	5B2	+ 3 mg/kg ipi	5C	+ 960 mg q12h vem	
10	6A	10	6A2	10	6B1	+ 3 mg/kg ipi	6B2	+ 3 mg/kg ipi	6C	+ 960 mg q12h vem	
30	7A	30									
10					7B1	+ 6 mg/kg ipi	7B2	+ 6 mg/kg ipi			

[1]The Sponsor in consultation with the SRC may modify the doses of study drug in response to DLTs observed during the study.

Figure 4: Phase 1/2a Dose Escalation, Dose Expansion, and Response Evaluation Schema



PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; q2wk = every 2 weeks; SRC = Safety Review Committee.

6.1. Dose Limiting Toxicities and Late Stopping Rules

6.1.1. Dose Limiting Toxicities

All AEs will be captured according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 and considered DLTs as outlined by the criteria in Table 4. The DLT evaluation period is 28 days (Parts A, B1, B2, and C).

Table 4: Dose Limiting Toxicity

Suspected DLT Criteria	DLT?	
	Yes	No
Grade 5 AEs	X	
Grade 4 AEs judged by the Investigator to be treatment-related or judged by the Sponsor as a DLT, regardless of Investigator-attribution* • Any Grade 4 endocrinopathy.	X	
***Exceptions** The following Grade 4 hematologic AEs: • Grade 4 lymphopenia; and • Grade 4 neutropenia lasting ≤ 48 hours that is not associated with fever or other clinically significant symptoms. Electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.		X
Grade 3 AEs judged by the Investigator to be treatment-related or by the Sponsor, regardless of Investigator-attribution: • Any Grade 3 central nervous system event, regardless of duration or reversibility.	X	
The following Grade 3 AEs will not be considered DLTs: • Nausea, diarrhea, asthenia, constipation, pyrexia, and vomiting that resolves within 48 hours with appropriate treatment; • Isolated Grade 3 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset; • Clinically manageable endocrinopathy; • "Tumor flare" – defined as local pain, irritation, or rash localized at sites of known or suspected tumor; and • AEs judged by the Investigator to be related only to vemurafenib without contribution of CX-072.		X
Grade 2 pneumonitis necessitating discontinuation of CX-072 is a DLT.	X	
Grade 2 ocular toxicity necessitating discontinuation of CX-072 is a DLT.	X	

AE = adverse event; DLT = dose limiting toxicity.

6.1.2. Late Stopping Rules for Parts A Through C

If ≥ 1 patient experiences ≥ Grade 4 CX-072–related AEs beyond the DLT evaluation period, further enrollment in that part of the study will not be permitted until a review by the SRC. In this situation, the SRC may recommend that further dosing in that part of the study be terminated; that further dosing may resume, but with added safety parameters; that dosing may continue, but only at lower doses; or that the regimen for drug administration be modified.

Implementation of these recommendations may result in a protocol amendment to ensure patient safety and, where required, can be implemented only after approval of an amended protocol. Implementation of these recommendations may require a substantial amendment in the participating EU Member States.

6.1.3. Safety Review Committee for Dose Escalation Parts

The SRC, comprised of at least 3 to 5 members, including participating Investigators and CytomX Medical Monitor(s), will monitor AE data. This committee will review available dosing and safety study data from the current and previous cohorts before providing recommendations related to dose escalation for the subsequent cohort. Recommendations to proceed with dose escalation, to modify the dose escalation schema, or modify the protocol related to patient oversight will be made by the SRC. Details on the SRC are provided in APPENDIX 4.

6.2. Part A: Dose Escalation of CX-072 Monotherapy and Imaging Substudy

The primary objectives of Part A are to assess safety, tolerability, and determine the MTD and DLTs of CX-072 when administered as monotherapy. Up to 33 patients naive to immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated) with any metastatic or advanced unresectable solid tumor or lymphoma who have failed SOC treatment may be enrolled in the dose escalation cohorts. Patients may have measurable or nonmeasurable disease.

CX-072 monotherapy will be administered at the following doses: 0.03, 0.1, 0.3, 1, 3, 10, and 30 mg/kg.

The DLT period for CX-072 monotherapy determination is 28 days. Each cycle of CX-072 monotherapy treatment is 8 weeks (see Figure 5).

Patients enrolled at the first 3 dosing cohorts (0.03, 0.1, and 0.3 mg/kg) who complete the DLT assessment period may have their dose of CX-072 increased to a higher dose level provided that the relevant dose level has successfully passed the DLT period and the patient has not already progressed on study drug.

Patients in the 0.03 mg/kg dosing cohort will be administered CX-072 by slow IV push over 3 to 5 minutes q2wk. Beginning with the 0.1 mg/kg cohort, CX-072 will be administered IV over 1 hour (0.1, 0.3, 1, 3, or 10 mg/kg) or ≥ 90 minutes (30 mg/kg) q2wk.

Figure 5: Part A: Monotherapy CX-072 Dosing

	DLT Period Days 1-28 of Cycle 1							
	Monotherapy Treatment CX-072 q2wk – 8 Week Cycles							
Part A	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 56
CX-072	X		X		X		X	

DLT = dose limiting toxicity; q2wk = every 2 weeks.

The first patient in each new dose escalation cohort will be dosed at least 1 day prior to any other patients in that cohort, to allow for observation of possible severe and/or serious acute (e.g., infusion-related) toxicities that might affect subsequent patient enrollment or dosing decisions.

Enrollment into each of the first 3 cohorts will initiate with 1 patient until the first 3 dose levels are enrolled and treated successfully or 1 patient experiences a DLT or a ≥ Grade 2 study drug-related AE, whereupon an additional 2 patients will be enrolled at that dose level. All subsequent dose levels will enroll in the 3 + 3 design. If no patient in the first 3 cohorts experiences a DLT or ≥ Grade 2 study drug-related AE following the completion of the DLT assessment period for dose level 3, the study will switch to a 3 + 3 design.

Enrollment into each subsequent cohort will be initiated with 3 patients. If none of the first 3 evaluable patients in a cohort experiences a DLT, that dose level will be deemed safe and another 3 patients will be treated at the next higher dose level. If 1 of the first 3 patients experiences a DLT, 3 more patients will be treated at the same dose level. The SRC will consider AEs, particularly severe immune toxicities that may have occurred in patients in any cohort even beyond the DLT period, when making decisions/recommendations to proceed to the next higher dose level.

The MTD is defined as the highest dose tested at which no more than 1 of 6 patients has experienced a DLT. When the MTD has been exceeded, a total of 6 patients must be enrolled in the previous dose tested and/or the stepdown dose to determine the MTD (see Table 5).

Monotherapy dose escalation/DLT dosing period must be successfully completed in Part A at the Part A2 dose level before enrollment into Part A2 at that same dose level may be initiated. Monotherapy dose escalation/DLT dosing period must be completed in subsequent cohorts in Part A before enrollment in Parts B1, B2, or C may be initiated (i.e., 0.3 mg/kg CX-072 plus 3 mg/kg of ipilimumab can only be enrolled after the 1 mg/kg monotherapy dose of CX-072 has been determined to be safe).

Patients who discontinue study drug administration for reasons other than DLT may be replaced to ensure the minimum number of patients required for DLT evaluation is enrolled. Patients who have enrolled in the study and have withdrawn prior to receiving the first dose will be designated as screen failures. These patients, as well as those who withdraw prior to completion of the DLT period for reasons other than toxicity, may be replaced.

Once monotherapy dose escalation is complete and the MTD or MAD has been determined for CX-072, monotherapy expansion may be initiated for an imaging substudy. The Part A monotherapy imaging substudy will only be performed at up to 3 sites in the Netherlands and will allow enrollment of up to 22 additional patients at a recommended dose of 10 mg/kg CX-072. The imaging substudy will allow evaluation of the uptake of the tracer in the tumor lesions and whole body distribution leading to new insights about Probody therapeutic binding across lesions and patients and to relate these findings to subsequent treatment effects and toxicity. Part D monotherapy expansion will enroll patients with UPS, small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, TNBC with skin lesions, and hTMB and will be initiated at a fixed dose of 10 mg/kg. [redacted]

[redacted]

In order for a given dose to be "completed," the proportion of patients experiencing a DLT during monotherapy dose escalation may not exceed 33% with the rules outlined in Table 5.

Table 5: Part A Monotherapy: Dose Escalation Rules

# Patients in Cohort	# DLTs/ # Patients	Action
1	0/1	Dose completed
1	1/1	Add 2 additional patients to the cohort; all subsequent cohorts 3 + 3 design
3	0/3	Dose completed
3	1/3	Add 3 additional patients to the cohort
3	≥ 2/3	Dose level is above the MTD, escalation ceases
6	1/6	Monotherapy dose is completed
6	≥ 2/6	Dose level is above the MTD, escalation ceases

= number; DLT = dose limiting toxicity; MTD = maximum tolerated dose.

6.2.1. CX-072 Monotherapy Expansion for Imaging Substudy

Once monotherapy dose escalation is complete and the MTD or MAD has been determined for monotherapy CX-072, monotherapy expansion for imaging substudy may be initiated. The monotherapy expansion for imaging substudy will only be performed at up to 3 sites in the Netherlands and will allow enrollment of up to 22 additional patients at a recommended dose of 10 mg/kg CX-072. The primary objective of this substudy is to evaluate the whole body distribution of zirconium-89 (^{89}Zr)-CX-072 in patients with locally advanced or metastatic solid tumors or malignant lymphoma. Radiolabeling of CX-072 with the positron emission tomography (PET) radionuclide ^{89}Zr enables serial non-invasive imaging and quantification of distribution of ^{89}Zr-CX-072. By performing ^{89}Zr-CX-072-PET scans prior to initiation of CX-072 treatment as part of the main study, whole body distribution and ^{89}Zr-CX-072 can be evaluated and compared to treatment response and toxicity during treatment.

For further details, refer to the CTMX-M-072-001 Substudy Protocol. The imaging substudy for this trial was closed to new patient enrollment in 2019.

6.3. Part A2: CX-072 Monotherapy Dose Effect

The primary objective of Part A2 is to obtain a gauge of the relationship between dose/exposure and PD, safety, and efficacy. Up to 24 patients will be enrolled at 4 dose levels with up to 6 patients per cohort dose. In each cohort, at least 2 patients must have TET. Patients must be immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated), and have a TPS ≥ 1% membranous staining based on the DAKO PD-L1 IHC 22C3 pharmDX. Patients must have measurable disease.

CX-072 monotherapy will be administered at the following doses: 0.3, 1, 3, and 10 mg/kg.

Patients will be administered CX-072 IV infused over 1 hour (0.3, 1, 3, and 10 mg/kg) q2wk. See Figure 5 for monotherapy CX-072 dosing.

Each cohort's enrollment into Part A2 may only be initiated after successful completion of the Part A CX-072 monotherapy at that same dose level.

Six patients must be enrolled into each cohort before the next sequential cohort can be enrolled. All available safety data in Part A2 will be considered by the SRC.

If at any time more than 1/3 of patients experiences a DLT, further enrollment will be halted until a review by the SRC. In this situation, the SRC may recommend that further dosing in that part of the study be terminated; that further dosing may resume, but with added safety parameters; that dosing may continue, but only at lower doses; or that the regimen for drug administration be modified. Implementation of these recommendations may result in a protocol amendment to ensure patient safety.

Patients who have enrolled in the study and have withdrawn prior to receiving the first dose will be designated as screen failures and be replaced.

Intra-patient dose escalation is permitted for patients enrolling in Cohorts 3A2 (0.1 mg/kg), 4A2 (0.3 mg/kg), and 5A2 (3 mg/kg) with TET that have stable disease (SD) and have not experienced an immune-related AE (irAE). If a higher dose level has cleared the DLT period and the SRC judges the dose level as safe, intra-patient dose escalation will be permitted to higher dose levels, after consultation with the Medical Monitor, but only for patients in the first dose levels (0.3 mg/kg, 1 mg/kg, and 3 mg/kg). Patients may be allowed more than 1 dose escalation to reach the dose of 10 mg/kg.

6.4. Part B1: CX-072 Administered in a Concomitant Combination Schedule with Ipilimumab

The primary objectives of Part B1 are to assess the safety and tolerability and to determine the MTD and DLTs of CX-072 when administered in a concomitant combination schedule with ipilimumab. Up to 30 patients naive to immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated) with any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) who have failed SOC treatment may be enrolled. Patients may have measurable or nonmeasurable disease.

Patients will be administered CX-072 IV infused over 1 hour (0.3, 1, 3, or 10 mg/kg), followed by ipilimumab (3 or 6 mg/kg) IV infused over 90 minutes q3wk for 4 doses. Following the completion of the combination treatment period, patients will continue to receive CX-072 q2wk.

The DLT period for CX-072 plus ipilimumab combination therapy dose escalation is 28 days. Combination therapy will be administered for Cycle 1 and Cycle 2 (11 weeks of combination therapy). Cycle 1 of CX-072 plus ipilimumab combination treatment is 6 weeks, and Cycle 2 of CX-072 plus ipilimumab combination treatment is 5 weeks. Cycles of CX-072 monotherapy will then commence, and each cycle of CX-072 monotherapy treatment is 8 weeks (see Figure 6).

A maximum of 4 doses of ipilimumab may be administered to any patient.

Figure 6: Parts B1 and B2: Combination Dosing CX-072 Plus Ipilimumab

	Combination DLT Period Days 1-28 of Cycle 1																
	Combination Treatment CX-072 + ipilimumab q3wk - one 6 Week Cycle (Cycle 1)						Combination Treatment CX-072 + ipilimumab q3wk - one 5 Week Cycle (Cycle 2)						Monotherapy Treatment CX-072 q2wk - 8 Week Cycles (Cycles 3-n)				
Parts B1 and B2	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64	Day 71	Day 77	Day 1	Day 15	Day 29	Day 43	Day 56
CX-072	X			X			X			X			X	X	X	X	
ipilimumab	X			X			X			X			D/C				

D/C = discontinue; DLT = dose limiting toxicity; qXwk = every X weeks.

Enrollment into Part B1 may only be initiated after the subsequent monotherapy dose level in Part A has successfully passed the monotherapy DLT dosing period.

The first patient in each new dose escalation cohort will be dosed at least 1 day prior to any other patients in that cohort, to allow for observation of possible severe and/or serious acute (e.g., infusion-related) toxicities that might affect subsequent patient enrollment or dosing decisions.

Enrollment will be initiated in each cohort with 3 patients. If none of the first 3 evaluable patients in a cohort experiences a DLT, that dose level will be deemed safe and another 3 patients will be treated at the next higher dose level. If 1 of the first 3 patients experiences a DLT, 3 more patients will be treated at the same dose level (see Section 6.1). The SRC will consider AEs, particularly severe immune toxicities that may have occurred in patients in any cohort even beyond the DLT period, when making decisions/recommendations to proceed to the next higher dose level.

The MTD is defined as the highest dose tested at which no more than 1 of 6 patients has experienced a DLT. When the MTD has been exceeded, a total of 6 patients must be enrolled in the previous dose tested and/or stepdown dose to determine the MTD (see Table 6).

Patients who discontinue study drug administration for reasons other than DLT may be replaced to ensure the minimum number of patients required for evaluation of the combination are enrolled. Patients who have enrolled in the study and have withdrawn prior to receiving the first dose of CX-072 will be designated as screen failures. These patients, as well as those who withdraw prior to completion of the DLT period for reasons other than toxicity, may be replaced.

In order for a given combination dose to be "completed," the proportion of patients experiencing a DLT during monotherapy dose escalation may not exceed 33% with the rules outlined in Table 6.

Table 6: 3 + 3 Dose Escalation Rules

# Patients in Cohort	# DLTs/ # Patients	Action
3	0/3	Dose completed
3	1/3	Add 3 additional patients to the cohort
3	≥ 2/3	Dose level is above the MTD, escalation ceases
6	1/6	Combination dose level is completed
6	≥ 2/6	Dose level is above the MTD, escalation ceases

= number; DLT = dose limiting toxicity; MTD = maximum tolerated dose.

The following conditions must be met before any patient can receive ipilimumab within a given combination cohort:

- The administration of the subsequent dose of CX-072 as monotherapy in Part A must have successfully passed the DLT safety assessment period, prior to opening a new cohort; and
- The addition of ipilimumab to the regimen is clinically acceptable in the judgment of the Investigator.

Determination of the monotherapy MTD will be a trial priority. As the eligibility criteria for Parts A and B1 are similar, patients will be preferentially enrolled into open slots for Part A. Part B1 will enroll patients when Part A does not have available slots or has been completed.

6.5. Part B2: CX-072 Administered in a Concomitant Combination Schedule with Ipilimumab

Prior to Amendment 6, patients enrolled and dosed in Part B2 received 4 doses of CX-072 monotherapy during a run-in period followed by 4 doses of CX-072 in combination with ipilimumab; patients then continued to receive CX-072 monotherapy. Previously in Part B2, CX-072 was dosed as a monotherapy run-in for 8 weeks without showing any significant effect prior to receiving their first dose of ipilimumab. As such, beginning with Amendment 6, the dose schedule has been changed to concomitant administration of CX-072 and ipilimumab. The primary objectives of Part B2 are to assess the safety and tolerability and to determine the MTD and DLTs of CX-072 when administered in a concomitant combination schedule with ipilimumab. Up to 18 patients naive to CTLA-4 inhibitors and with prior therapy with PD-1/PD-L1 inhibitors, discontinued for reasons other than toxicity, with any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) with measurable disease will be enrolled. Patient biopsies are mandatory in cohorts receiving CX-072 + 3 mg/kg ipilimumab (but not patients receiving 6 mg/kg ipilimumab).

Patients will be administered CX-072 IV infused over 1 hour (3 or 10 mg/kg), followed by ipilimumab (3 or 6 mg/kg) IV infused over 90 minutes q3wk for 4 doses. Following the completion of the combination treatment period, patients will continue to receive CX-072 q2wk.

The DLT period for CX-072 plus ipilimumab combination therapy dose escalation is 28 days. Combination therapy will be administered for Cycle 1 and Cycle 2 (11 weeks of combination therapy). Cycle 1 of CX-072 plus ipilimumab combination treatment is 6 weeks, and Cycle 2 of CX-072 plus ipilimumab combination treatment is 5 weeks. Cycles of CX-072 monotherapy will then commence, and each cycle of CX-072 monotherapy treatment is 8 weeks (see Figure 6).

A maximum of 4 doses of ipilimumab may be administered to any patient in Part B2.

The first patient in each new dose escalation cohort will be dosed at least 1 day prior to any other patients in that cohort, to allow for observation of possible severe and/or serious acute (e.g., infusion-related) toxicities that might affect subsequent patient enrollment or dosing decisions.

Enrollment will be initiated in each cohort with 3 patients. If none of the first 3 evaluable patients in a cohort experiences a DLT, that dose level will be deemed safe and another 3 patients will be treated at the next higher dose level. If 1 of the first 3 patients experiences a DLT, 3 more patients will be treated at the same dose level (see Section 6.1). The SRC will consider AEs, particularly severe immune toxicities that may have occurred in patients in any cohort even beyond the DLT period, when making decisions/recommendations to proceed to the next higher dose level.

The MTD is defined as the highest dose tested at which no more than 1 of 6 patients has experienced a DLT. When the MTD has been exceeded, a total of 6 patients must be enrolled in the previous dose tested and/or stepdown dose to determine the MTD (see Table 6).

Patients who discontinue study drug administration for reasons other than DLT may be replaced to ensure the minimum number of patients required for evaluation of the combination are enrolled. Patients who have enrolled in the study and have withdrawn prior to receiving the first dose of CX-072 will be designated as screen failures. These patients, as well as those who withdraw prior to completion of the DLT period for reasons other than toxicity, may be replaced.

In order for a given combination dose to be "completed," the proportion of patients experiencing a DLT during monotherapy dose escalation may not exceed 33% with the rules outlined in Table 6.

The following conditions must be met before any patient can receive ipilimumab within a given combination cohort:

- The administration of the subsequent dose of CX-072 as monotherapy in Part A must have successfully passed the DLT safety assessment period, prior to opening a new cohort; and
- The addition of ipilimumab to the regimen is clinically acceptable in the judgment of the Investigator.

6.6. Part C: Dose Escalation of CX-072 Plus Vemurafenib Combination

Part C will enroll up to 18 patients naive to BRAF-inhibitors and naive to immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy is not available to the patient) with measurable or nonmeasurable BRAF V600E mutation-positive metastatic or advanced unresectable melanoma. The primary objectives for Part C are to assess the safety, tolerability, and determine the MTD and DLTs of CX-072 in combination with vemurafenib. Patients will receive an IV infusion of CX-072 over 1 hour (1, 3, or 10 mg/kg) q2wk with oral vemurafenib 960 mg taken PO twice daily (approximately q12h).

The DLT period for CX-072 plus vemurafenib combination therapy dose escalation is 28 days. Each cycle of CX-072 plus vemurafenib combination treatment is 8 weeks (see Figure 7).

Enrollment into Part C may be initiated only after the subsequent CX-072 monotherapy cohort in Part A has been completed and deemed safe by the Sponsor in consultation with the SRC.

Figure 7: Part C: Combination CX-072 Plus Vemurafenib Dosing

	DLT Period Days 1-28 of Cycle 1							
	Combination Treatment CX-072 q2wk + vemurafenib q12h daily – 8 Week Cycles							
Part C	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 56**
CX-072	X		X		X		X	
vemurafenib	Orally q12h daily							

DLT = dose limiting toxicity; q12h = every 12 hours; q2wk = every 2 weeks.

The first patient in each new dose escalation cohort will be dosed at least 1 day prior to any other patients in that cohort, to allow for observation of possible severe and/or serious acute (e.g., infusion-related) toxicities that might affect subsequent patient enrollment or dosing decisions.

Enrollment will be initiated in each cohort with 3 patients. If none of the first 3 evaluable patients in a cohort experiences a DLT, that dose level will be deemed safe and another 3 patients will be treated at the next higher dose level. If 1 of the first 3 patients experiences a DLT, 3 more patients will be treated at the same dose level. The SRC will consider AEs, particularly severe immune toxicities that may have occurred in patients in any cohort even beyond the DLT period, when making decisions/recommendations to proceed to the next higher dose level.

Each new cohort of 3 patients may be initiated only after the previous CX-072 plus vemurafenib DLT review period has been completed and deemed safe by the Sponsor in consultation with the SRC and provided that the subsequent dose of CX-072 monotherapy has also been deemed to be safe in Part A.

The MTD is defined as the highest dose tested at which no more than 1 of 6 patients has experienced a DLT. When the MTD has been exceeded, a total of 6 patients must be enrolled in the previous dose tested and/or stepdown dose to determine the MTD (see Table 6).

Patients who discontinue study drug administration, for reasons other than DLT, may be replaced to ensure the minimum number of patients required for evaluation of the combination is enrolled.

Patients who have enrolled in the study and have withdrawn prior to receiving the first dose will be designated as screen failures. These patients, as well as those who withdraw prior to completion of the DLT period for reasons other than toxicity, may be replaced. Patients that did not experience a DLT but were administered < 80% of the vemurafenib will be considered nonevaluable for DLT and may be replaced.

6.7. Part D: Dose Expansion of CX-072 Monotherapy in Patients with Specific Tumor Types

Following the completion of the monotherapy dose escalation, specific tumor types will be enrolled in dose expansion to have the opportunity to observe the efficacy and safety of CX-072 in these specific populations.

CX-072 monotherapy will be administered at doses of 10 mg/kg, determined in Part A, q2wk. Each cycle of CX-072 monotherapy treatment is 8 weeks. See Figure 5 for monotherapy CX-072 dosing. As noted in Table 7, the first 14 evaluable patients (small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, and TNBC with skin lesions) and 20 evaluable patients (UPS) will be assessed for requisite antitumor activity prior to expansion.

The SRC will evaluate safety data from Part D and make recommendations regarding safety on an ongoing basis no less than monthly. For Part D, DLTs will not be formally assessed as in Parts A, A2, B1, B2, and C. When reviewing the safety data the SRC will pay particular attention to higher grade events and AESIs.

6.7.1. Undifferentiated Pleomorphic Sarcoma

UPS (previously referred to as malignant fibrous histiocytoma) is an aggressive sarcoma of the soft tissue or bone with an incidence of approximately 1 new case per 100,000 people per year. SOC for UPS is surgery and/or radiation. Patients with metastatic, inoperable, or advanced recurrent or persistent UPS have a poor prognosis, which is reflected by a median survival of 12 months after development of distant metastases, irrespective of the systemic treatment chosen (Linch 2014). Thus, there is an unmet medical need for novel therapy.

PD-L1 expression is potentially elevated in UPS, with prognostic significance. In one series (Pollack 2017), 16/20 patients with UPS expressed PD-L1 (2+ to 4+) in the TME using a noncommercial laboratory-based assay. High expression of genes that were related to both antigen presentation and T-cell mediated immunity (as characterized by nanostring) was a common finding in UPS. High PD-L1 expression was associated with higher grade disease and PD-1+ T-cell infiltrate. While detectable PD-L1 was noted in a variety of subsets of soft tissue sarcoma, UPS had higher levels of PD-L1 expression compared to the other types evaluated ($p=0.001$) and PD-1 expression compared to other sarcoma subtypes ($p=0.05$).

Another series of soft tissue sarcomas analyzed by Kim 2013 included 11 UPS with PD-L1 expression in 9/11 (82%) patients.

The ORR of pembrolizumab in UPS is compelling with 4/10 patients achieving an objective response, including 1 complete remission (Burgess 2017).

Furthermore, increased protease dysregulation has been demonstrated in soft tissue sarcoma, (Yang 2014) reinforcing the potential of the Probody therapeutic to be activated locally in the tumor.

6.7.2. Small Bowel Adenocarcinoma

Malignancies involving the small intestine are rare. Small bowel adenocarcinoma accounts for approximately 10,470 new cases and 1450 patient deaths annually in the United States (US) (Siegel 2018). Although the small intestine represents approximately 75% of the length and over 90% of the surface area of the alimentary tract, small bowel malignancies account for only 3% of all GI tract neoplasms and approximately 0.5% of all cancers in the US (Neugut 1998; Arparicio 2014; Siegel 2018).

Adenocarcinomas represent from 25% to 40% of small bowel cancers and usually present between the ages of 50 to 70 years, with a slight male predominance (Arparicio 2014). The incidence of adenocarcinoma is highest in the duodenum and decreases progressively throughout the rest of the small intestine. In a large single-institution study, records from 217 patients with small bowel adenocarcinoma were reviewed and 52% of the tumors occurred in the duodenum (Dabaja 2004).

Currently there is no approved first-line regimen for the treatment of advanced small bowel adenocarcinoma. Systemic chemotherapy has utilized a fluoropyrimidine plus platinum combination therapy based on treatment for metastatic colorectal cancer. However, the response to standard chemotherapy regimens has been mixed, with response rates ranging from 18% and 8 months median survival with combination of 5-fluorouracil (5-FU), mitomycin C, and doxorubicin, to 50% with an OS of 15.5 months with a regimen of capecitabine combined with oxaliplatin (CAPOX) (Overman 2009; Xiang 2012).

While there have not been any clinical trials using immunotherapy drugs specifically for small bowel adenocarcinoma, 2 separate studies on archived tumor samples from patients with small bowel adenocarcinomas showed high expression of PD-L1 in 53% to 83% of cases (Pedersen 2015; Thota 2017). This high expression of PD-L1 suggests a strong potential for PD-L1 inhibitor treatment in small bowel adenocarcinoma.

6.7.3. Cutaneous Squamous Cell Carcinoma

cSCC is the second most common human skin cancer, with an estimated annual incidence of 186,157 to 419,843 cases in the US (Karia 2013). The vast majority of cSCC is readily treated with local excision and cure; however, locoregional or distant metastases develop in 1.9% to 2.6% of cases (Brougham 2012). Because of its rarity, few therapeutic trials are available for patients with metastatic or locally advanced unresectable cSCC and no SOC has been established.

Chemotherapeutic agents such as cisplatin, 5-FU, capecitabine, methotrexate, cetuximab, bleomycin, and doxorubicin have been utilized in patients with metastatic or locally advanced cSCC that cannot be managed with surgical excision or radiation therapy. Data demonstrating efficacy are limited (NCCN Guidelines 2017).

Preliminary data from some small studies with antibodies or small molecules that target the epidermal growth factor receptor (EGFR) have demonstrated potential efficacy in patients with advanced cSCC, but similar to the conventional chemotherapeutic agents, it is not clear if these drugs improve outcomes in patients with distant metastatic cSCC. A Phase 2 study was conducted in 36 patients with cSCC treated with cetuximab, an anti-EGFR antibody, administered 400 mg/m^2 on week 1 and then 250 mg/m^2 weekly (Maubec 2011). Most patients

had locoregional disease and 8% had systemic metastases. The ORR was 28% with 8 patients experiencing a PR and 2 experiencing a CR. Fifteen patients had SD for an overall disease control rate of 69%. Three patients underwent complete resection of their tumor following treatment with cetuximab. In another small study, 16 patients with cSCC not suitable for local therapy were treated with panitumumab (6 mg/kg q2wk) (Foote 2014). An ORR was observed in 5 (31%) patients, including 3 (19%) patients with a PR, and 2 (12%) patients with a CR. In a small Phase 2 study, 40 patients with incurable cSCC were treated with gefitinib, an oral inhibitor of EGFR at a dose of 250 mg daily (William 2017). A modest ORR of 16% was observed (6 PR in 37 evaluable patients). An additional 13 (35%) patients had SD at 8 weeks. The median durations of response and PFS were 31.4 months (95% confidence interval [CI], 3.91%-not applicable) and 3.8 months (95% CI, 2.2%-5.7%), respectively.

Promising data from patients with head and neck SCC and melanoma have led to research into treating cSCC patients with immunotherapy, particularly with antibodies directed against PD-1 or its ligand PD-L1. The most extensive data to date come from a prospective Phase 1 expansion cohort using the experimental anti–PD-1 antibody cemiplimab (REGN2810) 3 mg/kg IV q2wk for up to 48 weeks. This study included 26 patients, 10 with metastatic disease and 16 with unresectable, locally advanced, cSCC (Papadopoulos 2018). The updated overall ORR was 46%, with 2 CR (7.7%) and 10 PR (38.5%). The disease control rate was 69.2%. A Phase 2 study with 82 patients with advanced cSCC (EMPOWER-CSCC) has just been completed and initial reports suggest a 46% ORR, similar to the Phase 1 study. In September 2018, cemiplimab-rwlc, a mAb that binds to PD-1, received FDA approval as the first and only treatment for metastatic or locally advanced cSCC. This suggests the potential for PD-L1 inhibitor treatment in cSCC.

6.7.4. Merkel Cell Carcinoma

MCC of the skin is a rare, aggressive cutaneous malignancy with an estimated 1600 cases per year in the US and predominantly affects elderly Caucasians (Albores-Saavedra 2010). MCC is lethal in 33% of cases and carries a worse prognosis than malignant melanoma (Hodgson 2005).

Surgery and/or radiation therapy may be curative for patients with locoregional MCC without metastases. Systemic chemotherapy (e.g., platinum-based therapy) has demonstrated high response rates (approximately 60%) in patients with metastatic disease, but the DOR is short (3 to 6 months) (Tai 2000; Bhatia 2011).

With the discovery of the association with Merkel cell polyomavirus (MCPyV) and expression of high levels of PD-L1 in MCC tumors (Lipson 2013), immunotherapy directed against the PD-1 pathway has been used as an appropriate alternative to systemic chemotherapy. In March 2017, avelumab, a mAb that binds to PD-L1, was the first drug to receive FDA approval for the treatment of MCC in adult and pediatric patients. In a Phase 2 clinical trial, 88 patients who had received prior chemotherapy were treated with avelumab (10 mg/kg q2wk) (Kaufman 2016). There were 28 objective responses (32%), including 8 CRs (9%). Responses appeared to be durable, and the PFS and OS at 6 months were 40% and 69%, respectively. An exposure-response relationship for efficacy was noted for avelumab in MCC suggesting a higher dose than avelumab 10 mg/kg q2wk may be more efficacious; however, this evaluation was based on limited data from a single-arm trial (FDA BLA 761049 2016). In September 2017, the European Union approved avelumab as monotherapy for treatment of metastatic MCC.

Two other immunotherapy agents that target the PD-1 pathway, pembrolizumab and nivolumab, have also shown evidence of activity in patients with metastatic MCC. In a Phase 2 study, 26 patients who were systemic therapy-naive were treated with pembrolizumab (2 mg/kg q3wk) (Nghiem 2016), and objective responses were observed in 14 of 25 evaluable patients (56%), including 4 CRs and 10 PRs. With a median follow-up of 33 weeks, only 2 of 14 patients (14%) had relapsed, and the 6-month rate of PFS was 67%. Furthermore, responses were observed in patients with MCPyV-positive tumors (62%) as well as in patients whose tumors were virus negative (44%). A case report in a 42-year old Hispanic man documented a marked reduction in tumor burden on nivolumab (3mg/kg q2wk) after only 4 cycles of treatment (Mantripragada 2015). This suggests the potential for PD-L1 inhibitor treatment in MCC.

6.7.5. Thymic Epithelial Tumors

TET are rare epithelial neoplasms arising in anterior mediastinum either as thymoma or thymic carcinoma with an incidence of 0.13/100,000 persons per year in the US (Engels 2010). Thymomas are indolent with a tendency toward local recurrence rather than metastasis. Thymic carcinomas are typically invasive, with a higher risk of relapse and death (Ogawa 2002). There are no known risk factors. For thymomas, there is a strong association with myasthenia gravis and other paraneoplastic syndromes (Safieddine 2014).

There are currently no FDA-approved drugs to treat TET and no randomized clinical trials that provide guidance for therapy in these patients. Surgical resection of the thymus is typically the SOC (NCCN Guidelines 2018; Gomez 2011). The stage of the tumor determines whether the patient receives post-operative radiation therapy with or without chemotherapy. The typical chemotherapy regimen for first-line treatment may include cyclophosphamide, doxorubicin, and cisplatin or cisplatin and etoposide for TET if chemotherapy is given on its own. If chemotherapy is given concurrently with radiation therapy, the preferred regimen is etoposide or carboplatin and paclitaxel. A wide range of agents have been used when disease progression occurs despite treatment with front-line options, including sunitinib, everolimus, etoposide, ifosfamide, pemetrexed, octreotide, 5-FU plus leucovorin, gemcitabine, and paclitaxel (NCCN Guidelines 2018).

Recently it has been shown that 70% of thymomas and 23% of thymic carcinomas express PD-L1, suggesting therapy with anti–PD-1/PD-L1 drugs could be of potential benefit in patients with locally advanced, unresectable, or recurrent disease. Data from a small single-center Phase 2 trial has shown that 41 thymic carcinoma patients who had progressed after receiving at least 1 prior line of chemotherapy achieved a 22.5% overall response rate when treated with 200 mg pembrolizumab q3wk up to 2 years (Giaccone 2018). The median DOR was 22.4 months (95% CI, 12.3%-34.7%), which is longer than patients who received the SOC therapy (i.e., sunitinib was 16.4 months). This suggests the potential for PD-L1 inhibitor treatment in TET.

6.7.6. Anal Squamous Cell Carcinoma

Anal SCC comprises 2.5% of all digestive system malignancies in the US; 8600 new cases are diagnosed annually (Siegel 2018). The incidence of anal cancer in the general population has increased over the last 30 years. From an etiologic standpoint, anal cancer is more similar to genital malignancies than it is to other GI tract cancers. Epidemiologic and clinical studies show that anal cancer is closely associated with human papillomavirus infection (Tilston 1997).

Primary treatment for patients with metastatic anal carcinoma is 5-FU with cisplatin, carboplatin/paclitaxel with or without radiation therapy, or FOLFOX with or without radiation therapy.

Recently, results with 2 immune checkpoint inhibitors that target the PD-1 pathway, nivolumab and pembrolizumab, have been reported in advanced anal SCC. In a small, prospective, Phase 2 trial conducted in patients with chemorefractory metastatic anal SCC, nivolumab was administered at a dose of 3 mg/kg IV q2wk (Morris 2017). Of the 37 patients, 9 (24%) patients had an objective response, 2 (5.4%) patients had a CR, 7 (19%) patients had a PR, and 17 (46%) patients had SD as best response. Median PFS was 4.1 months, and median OS was 11.5 months. Although the data were very limited (n = 13 patients), overexpression of PD-1 and PD-L1 seemed to correlate with responses.

In the KEYNOTE-028 trial, 25 patients with PD-L1-positive anal cancer were administered pembrolizumab at a dose of 10 mg/kg q2wk for up to 2 years (Ott 2017). Among the 24 patients with SCC histology, there were 4 confirmed PRs (overall response rate 17%) and an additional 10 (42%) patients had SD as the best response. This suggests the potential for PD-L1 inhibitor treatment in anal SCC.

6.7.7. Triple Negative Breast Cancer

TNBC lacks expression of the 3 most commonly evaluated biomarkers (ER, progesterone receptor, and human epidermal growth factor receptor 2 [HER2] protein). TNBC accounts for about 15% to 20% of breast cancers, tends to be more aggressive than other breast cancer types, and is more common in African-American women and women under 40 years old (Curigliano 2011; Gonzalez-Angulo 2011; Penault-Llorca 2012; Dietze 2015).

Many of the general principles applicable to advanced breast cancer of other phenotypes apply to TNBC. The 2014 ESO-ESMO guideline recommends anthracycline and taxane-based chemotherapy as initial treatment for locally advanced, noninflammatory TNBC (Cardoso 2014). For TNBC patients who are breast cancer gene (BRCA) mutation carriers, response rates and PFS are superior with first-line platinum treatment, but platinum drugs have not been shown to be effective in non-BRCA patients. Treatment of TNBC with standard chemotherapy often results in a short-lived response and is associated with significant toxicities (Gucalp 2011).

There are several drugs in clinical trials for the treatment of TNBC. Many are therapies that target specific mutations or signaling pathways (Jamdade 2015). Immunotherapy has been shown to be effective in solid tumors, especially in tumors that tend to be more immunogenic such as TNBC. Early studies with 2 drugs that inhibit PD-1/PD-L1, pembrolizumab and avelumab, have shown mixed results in patients with TNBC.

Pembrolizumab was used to treat patients with TNBC in 2 studies, KEYNOTE-012 and KEYNOTE-086 (Nanda 2016; Adams, Loi 2017; Adams, Schmid 2017). In the KEYNOTE-012 study, 32 TNBC patients positive for PD-L1 expression were treated with pembrolizumab 10 mg/kg IV q2wk. There was an overall response rate of 18.5% in the evaluable patients, with a median TTR of 17.9 weeks (7.3 to 32.4) (Nanda 2016). In the KEYNOTE-086 study, there were 2 cohorts of TNBC patients treated with 200 mg pembrolizumab IV q3wk. Cohort A enrolled 170 TNBC patients with and without PD-L1 expression who received prior treatment. Cohort B enrolled 52 TNBC patients positive for PD-L1 expression who had not received any prior treatment. In this study, the response rate was 5% for patients who received prior treatment

(regardless of PD-L1 expression) compared to a 23% response in PD-L1 positive patients who were not previously treated (Adams, Loi 2017; Adams, Schmid 2017).

In the JAVELIN solid tumor study, 58 patients with TNBC were treated with 10 mg/kg avelumab IV q2wk (Dirix 2018). The confirmed overall response rate was 5.2% with a higher response seen in patients who were PD-L1 positive.

For TNBC with skin lesions patients who have failed all SOC treatments, PD-L1 inhibitor treatment may have the potential to achieve response and clinical benefit in this difficult to treat population. Of note, in Part A, a 39-year-old female with TNBC was enrolled in the 10 mg/kg CX-072 q2wk cohort. At baseline, the patient's target lesions included 2 lymph nodes and a subcutaneous axillary nodule. On CX-072, the skin lesions resolved and the patient achieved a sustained PR in visceral lesions.

6.7.8. High Tumor Mutational Burden

Recently, data have been published showing a relationship between patients with hTMB and response to therapy with checkpoint inhibitors such as atezolizumab, nivolumab, and ipilimumab (Snyder 2014; Rosenberg 2016; Riaz 2017). In addition, tumor mutation load is associated with production of neoantigens, which may be recognized by the immune system, thereby enhancing a response to immune checkpoint inhibitors (Snyder 2014).

In a Phase 2 study, 310 patients with urothelial carcinoma who progressed following treatment with platinum-based therapy were treated with 1200 mg atezolizumab IV q3wk. Of the 310 patients, mutation load was estimated in 150 patients using tumor tissue collected during screening. There was a significantly higher median mutational load in patients who responded to treatment (12.4/ megabase [Mb]) compared to non-responders (6.4/Mb) ($p<0.0001$) (Rosenberg 2016).

Similarly, in melanoma patients treated with ipilimumab, there was a significant difference in mutational load between melanoma patients who received clinical benefit compared to those who received little to no clinical benefit ($p=0.01$) (Snyder 2014).

Recently, an assay to define tumor mutational burden in blood (bTMB) was validated using plasma samples from 2 different studies (POPLAR and OAK) in non-small cell lung cancer patients receiving the anti–PD-L1 agent, atezolizumab (Gandara 2017). The association between bTMB and atezolizumab efficacy was analyzed and the cut-point of ≥ 16 mutations/Mb was selected using samples from patients in the POPLAR study and validated using data from the OAK study. The results showed that bTMB ≥ 16 was associated with improved PFS and OS among patients treated with atezolizumab.

These data support the potential for PD-L1 inhibitor treatment in patients who have an hTMB.

7. PATIENT ENROLLMENT

Patients will be enrolled using an interactive web response system (IWRS). The investigative site will log into the IWRS to enroll a patient that meets eligibility for a part of the study. When multiple cohorts are open for enrollment, priority of enrollment into cohorts will be based on evaluation and verification of enrollment criteria (Section 10.1 and Section 10.2) for the various arms as follows:

- Part A > Part B1.
- Subjects eligible for Part B2 must be PD-L1 experienced and ineligible for Parts A, A2, B1, C, and D.
- Any subject with an advanced melanoma and known BRAF V600E mutation will be enrolled in Part C.

As soon as the recommended Phase 2 dose has been confirmed in Part A, subjects meeting the enrollment criteria for Part D will be enrolled.

Once assigned, numbers for any screening failures, nontreated, nonevaluable, or discontinued patients will not be re-used.

Under Amendment 6, enrollment cannot exceed the number specified in Stage 1 of the envisioned Simon 2-stage design as noted in Table 8. Opening of Stage 2 in this study is planned following discussions with regulatory authorities and an issuance of a subsequent protocol amendment.

8. STATISTICAL CONSIDERATION

8.1. Sample Size Determination

8.1.1. Sample Size Determination for Parts A Through C

Cohorts of 1, 3, or 6 patients may be treated at each dose level for Parts A, B1, B2, or C in the 3 + 3 design. The ultimate number enrolled to each study Part will depend on the observed safety at each cohort, where enrollment of additional patients (up to 6) may be required, as per protocol, to further elucidate the safety profile at a given dose level. Additionally, escalation may be halted before the highest planned dosing cohort is enrolled, should the MTD be defined at a lower dose.

Thus, the maximum number of patients enrolled to this study during dose escalation is as follows:

- In Part A, 15 to 33 patients may be enrolled (1 to 6 patients per cohort, up to 7 cohorts);
- In Part A2, 24 patients may be enrolled (6 patients per cohort, up to 4 cohorts);
- In Part B1, 15 to 30 patients may be enrolled (3 to 6 patients per cohort, up to 5 cohorts);
- In Part B2, 9 to 18 patients may be enrolled (3 to 6 patients per cohort, up to 3 cohorts); and
- In Part C, 9 to 18 patients may be enrolled (3 to 6 patients per cohort, up to 3 cohorts).

For Part A, an expansion cohort of up to 22 additional patients is planned to be enrolled for an imaging substudy conducted in the Netherlands.

[redacted]

8.1.2. Sample Size Determination for Parts D [redacted]

For the Part D expansion, potentially eligible patients will be those with: UPS, small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, TNBC with skin lesions, and hTMB for the purposes of providing preliminary assessment of response, as well as additional safety assessment at doses of 10 mg/kg. The expansion cohorts are enrolled in a gated fashion as explained below. The number of patients mentioned in the following discussion refers to treated

patients with measurable disease at baseline per RECIST v1.1. Response refers to confirmed objective response.

A total of 20 patients will be evaluated for UPS and 14 patients will be evaluated for small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, TNBC with skin lesions, and hTMB. [redacted] Patients of hTMB will be enrolled into Part D only for a total of 25 patients. As hTMB cohort may consist of multiple tumor types and therefore has greater uncertainty in terms of treatment benefit, an exploration based on 25 patients is warranted before further development in this indication. [redacted]

[redacted]

8.2. Statistical Analyses

Fatal AEs due to disease progression not considered related to study drug will be excluded from AE summaries.

8.2.1. Statistical Analyses for Parts A Through C

All available data from Part A2 will be pooled with data from Part A by dose. In addition, efficacy data from Part A2 may be analyzed separately. The relationship between dose and safety/efficacy may be explored. Analyses by dose may be conducted for, but not limited to, the following endpoints: frequency of AEs of special interest, ORR, and percent reduction in tumor burden by dose. A generalized linear model may be used to adjust for covariates or to model the relationship. Because of the limited number of patients, the above analyses will be conducted if data warrant.

Subgroup analyses will be conducted for TET patients. These will include, but not be limited to, listings of AEs and response assessment.

8.2.2. Statistical Analyses for Parts D [redacted]

Data for Parts D [redacted] will be analyzed by tumor type. In addition, safety data will be pooled across tumor types.

Descriptive summaries will be provided. For continuous measures, these will include mean, median, standard deviation, and range. For categorical measures, these will include counts and percentages.

The Intent-to-Treat (ITT) Population will include all enrolled patients who receive any amount of study drug. The Safety Analysis Population will include all enrolled patients who receive any amount of study drug. The Response Evaluable Population includes all subjects in the ITT Population who have measurable disease at baseline per RECIST v1.1.

The ITT Population will be used for analyses related to patient characteristics and disposition. The Safety Analysis Population will be used to summarize safety data including study drug exposure, laboratory data, and adverse events.

The Response Evaluable Population will be used to summarize efficacy data including ORR, DOR, TTR, PFS, and OS. Sensitivity analyses on ORR will be conducted based on the ITT Population, and patients in the Response Evaluable Population with at least 1 post-baseline disease assessment.

The discordance between the Investigator and IRF assessments on objective response will be summarized.

Objective response will be summarized by count and percentage. In addition, a 95% CI based on the method of Koyama and Chen (Koyama 2008) will be provided. This method is appropriate because it is proposed for Simon's 2-stage design, accounting for the inherent futility analysis.

DOR is defined as the time from the first documentation of objective response that is subsequently confirmed to the first documentation of disease progression as assessed by an IRF or death due to any cause on study, whichever occurs first. DOR is only calculated for patients who have a confirmed objective response. Patients who neither progress nor die will be censored on the date of their last tumor assessment. Patients who start subsequent anti-cancer therapy prior to progression will be censored on the date of their last tumor assessment prior to the initiation of subsequent anti-cancer therapy.

TTR is defined as the time from the date of the first dose of study drug to the first documentation of objective response as determined by an IRF. TTR is only calculated for patients who have a confirmed objective tumor response.

PFS is defined as the time from the date of the first dose of study drug to the date of the first documentation of disease progression as determined by an IRF or death due to any cause on study, whichever occurs first. Patients who die without disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study tumor assessments and did not die will be censored on their date of enrollment. Patients who start subsequent anti-cancer therapy prior to disease progression will be censored on the date of their last tumor assessment prior to the initiation of subsequent anti-cancer therapy.

OS is defined as the time from the date of the first dose of study drug to the date of death due to any cause on study.

Estimates of time-to-event endpoints (DOR, TTR, PFS, and OS) will be obtained using the Kaplan-Meier method. The median duration and its 95% CI based on Brookmeyer and Crowley method (Brookmeyer 1982) will be provided.

A separate statistical analysis plan (SAP) will be generated for Part E and additional details will be specified within the SAP. In instances where the SAP might contradict the analyses specified in the Common Core Document, the SAP supersedes the Common Core Document.

A retrospective central review will be conducted to confirm diagnosis for TET patients. Patients who are determined not to have TET by central review will be included in safety analyses but excluded from efficacy analyses for TET.

The following analyses may be conducted by tumor type: frequency of AEs of special interest (AESIs), irAEs, use of immune modulating agents, and discontinuation rate of treatment. Furthermore, the correlation of angiopoietin 2 and response and durability of response may be explored for each tumor type.

[redacted]

[redacted]

Additional statistical assessments/methods for safety, efficacy, PK/PD, and immunogenicity are found in the Common Core Document.

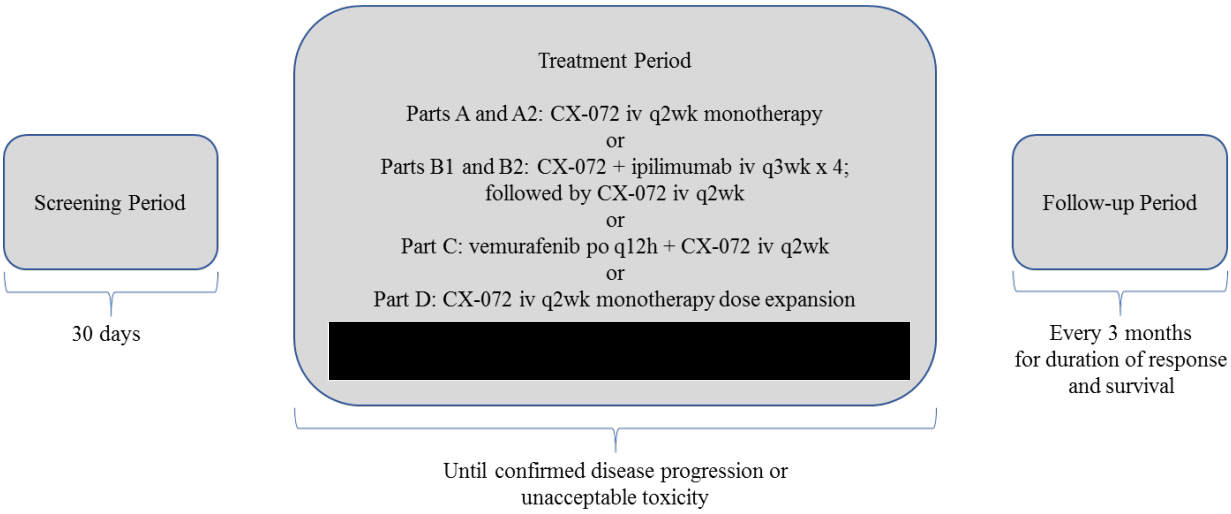
9. DURATION OF TREATMENT AND FOLLOW-UP

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points (see Figure 8). The schedule of study procedures summarizes the frequency and timing of efficacy, safety, and other study measurements. Results of tumor assessments must be reviewed and documented before administering the next study treatment.

A patient who is withdrawn from the study during a DLT assessment period before the completion of the assessment period for a reason other than DLT will be replaced.

An individual patient's participation in the study Parts A-E is approximately 2 years. Upon activation of Amendment 09, Investigators may elect to allow patients who continue to receive clinical benefit to continue to receive study drug if permitted by the Sponsor (see Section 19, Section 20, and Section 21).

Figure 8: Study Periods



iv = intravenous; po = oral; qXd = every X days; qXwk = every X weeks.

Following the completion of study treatment, patients with progressive disease will enter the follow-up period for monitoring of survival; patients with SD, PR, or CR will enter the follow-up period for monitoring of DOR and PFS. Once a patient experiences a withdrawal criterion (as outlined in Section 9.1), they will continue to be monitored for survival.

Once Protocol Amendment 09 is approved at a site, patients receiving study treatment will be eligible to roll over to the long-term extension part of the study (see Section 19 through Section 27). Patients who are no longer receiving study treatment but are in the follow-up period for Parts A-E will have concluded their participation in the study due to Sponsor termination. Follow-up for survival will no longer be performed.

9.1. Discontinuation of Patients from Treatment

Patients MUST discontinue investigational product (IP) (and non-IP at the discretion of the Investigator) for any of the following reasons:

- The patient experiences progression of disease by either RECIST or irRECIST guidelines; for a patient with a single observation of disease progression, the patient may continue until the next scheduled radiological assessment. If continued progression (>20% increase in target lesions, unequivocal progression in non-target lesions or new lesion(s) assessed by the Principal Investigator as likely representing new site(s) of malignant disease), the patient must be discontinued from the trial.
- The patient is unwilling or unable to adhere to the protocol.
- The patient withdraws consent or is lost to follow-up.
- The patient experiences an intercurrent illness that prevents further administration of IP and/or reference therapy.
- The patient experiences a DLT or an AE related to study drug(s) which precludes further administration of the study drug(s).
- The patient experiences a prolonged treatment delay (as defined in Section 12).
- The patient becomes pregnant, either prior to the first dose of study drug or at any time during treatment.
- In the Investigator's judgment, the patient should discontinue treatment.
- The Sponsor terminates the study.

9.2. Study Completion

For Parts A-E, the study will be completed approximately 2 years from when the last patient is enrolled, or when the last patient has completed treatment and the initial safety follow-up visit. For this trial, the last patient was enrolled on 16 September 2019.

Once Protocol Amendment 09 is approved at a site, patients receiving CX-072 study treatment will be eligible to roll over to the long-term extension part of the study, and Parts A-E of Study CTMX-M-072-001 will be considered to be terminated by the Sponsor for patients who are currently in the follow-up phase.

10. SELECTION OF PATIENTS

Up to 123 patients may be enrolled into the dose escalation cohorts (Parts A through C) and 195 patients into the expansion cohort (Part D), and 250 patients in Stage 1 of the envisioned Simon 2-stage design in Part E for a total of up to 568 patients (if every cohort is completely filled). The current amendment allows enrollment up to Stage 1 of Simon 2-stage design. In Part A, an expansion cohort of up to 22 additional patients is planned to be enrolled for an imaging substudy conducted in the Netherlands.

After signing the informed consent form (ICF) patients will be evaluated for CTMX-M-072-001 study eligibility during the Screening Period (no more than 30 days before study drug administration) according to the following inclusion/exclusion criteria.

10.1. Inclusion Criteria

Patients who fulfill the following criteria at screening will be eligible for admission into the study. All patients must have histologically confirmed diagnosis of metastatic or locally advanced unresectable tumors that progressed or are intolerant to standard therapy as defined below.

10.1.1. Inclusion Criteria for Patients in Part A

- Part A: any metastatic or advanced unresectable solid tumor or lymphoma, measurable or nonmeasurable disease allowed, no further SOC therapy available
    - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)

10.1.2. Inclusion Criteria for Patients in Part A2

- Part A2: any metastatic or advanced unresectable solid tumor or lymphoma (at least 2 patients in each cohort with TET), measurable disease allowed, no further SOC therapy available
    - TPS ≥ 1% membranous staining based on the DAKO PD-L1 IHC 22C3 pharmDx
    - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
    - Agreement to participate in biomarker analysis and have a tumor site that is safe to biopsy

10.1.3. Inclusion Criteria for Patients in Part B1

- Part B1: any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET), measurable or nonmeasurable disease allowed, no further SOC therapy available
    - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)

10.1.4. Inclusion Criteria for Patients in Part B2

- Part B2: any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) with measurable disease allowed, no further SOC therapy available
  - Previous treatment with a PD-1/PD-L1 inhibitor
  - Discontinued treatment with PD-1/PD-L1 inhibitor for reasons other than toxicity
  - Naive to treatment with a CTLA-4 inhibitor
  - Agreement to participate in biomarker analysis and have a tumor site that is safe to biopsy (only in cohorts receiving CX-072 + 3 mg/kg ipilimumab [but not 6 mg/kg ipilimumab])

10.1.5. Inclusion Criteria for Patients in Part C

- Part C: metastatic or advanced unresectable melanoma with BRAF V600E mutation-positive as detected by a diagnostic approved test (in the region where the patient is treated), measurable or nonmeasurable disease allowed
  - Naive to treatment with BRAF-inhibitor
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy is not available to the patient)

10.1.6. Inclusion Criteria for Patients in Part D

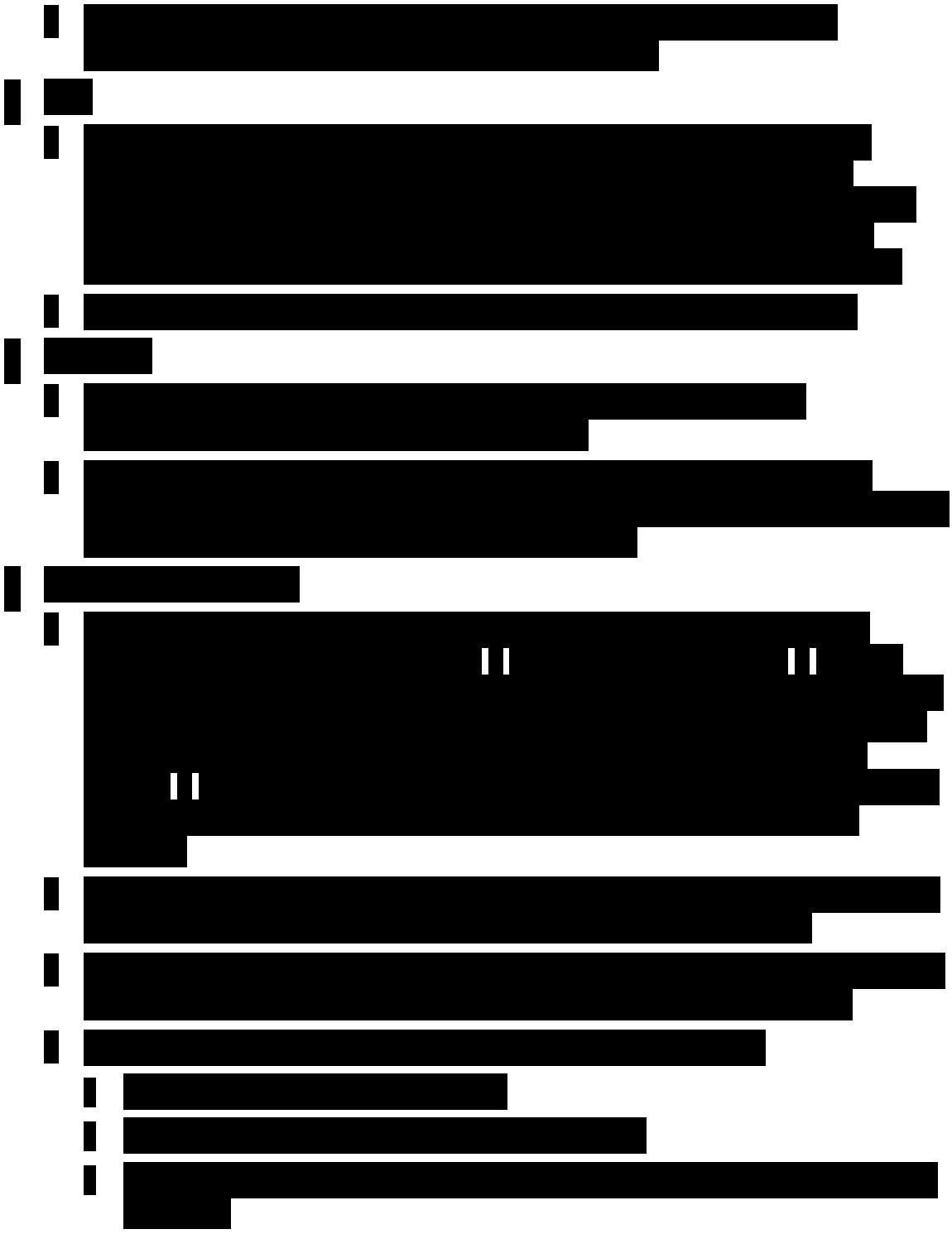
- Part D: measurable disease is required.
  - Must be willing to provide a blood sample at screening for hTMB testing
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no available life-prolonging immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy to the patient) of the following tumor types:
  - UPS
    - Metastatic or advanced unresectable UPS
    - TPS ≥ 1% membranous staining or unknown PD-L1 status
    - Patients must have had SOC surgery and/or radiation for their UPS; patients with metastatic disease should have received at least 1 prior systemic therapy according to local guidelines
  - Small bowel adenocarcinoma
    - Have metastatic or locally advanced unresectable small bowel adenocarcinoma of the duodenum, jejunum, ileum (excluding neuroendocrine, ampullary, and appendiceal tumors)

- Patients must have had at least 1and no more than 3 prior lines of systemic chemotherapy for metastatic or advanced unresectable disease; adjuvant therapy does not count as first-line therapy unless cancer recurs < 6 months after last administration of that regimen

- cSCC
  - Has metastatic or locally advanced unresectable primary cSCC;
- MCC
  - Metastatic or advanced unresectable MCC
  - Prior surgical resection was performed if resectable or potentially of benefit
  - Radiation therapy administered if of potential benefit with documented progression following completion of radiation therapy
- TET
  - Histologically confirmed diagnosis of TET (classified in accordance with 2015 World Health Organization criteria) with stage II, III, or IV disease per Masaoka-Koga 1994; details provided in APPENDIX 2
  - Received at least 1 prior chemotherapy regimen
- Anal SCC
  - Metastatic or locally advanced unresectable anal SCC
  - Must have had prior radiation therapy and/or chemotherapy treatment
- TNBC with skin lesions
  - Must have histologically confirmed ER, progesterone receptor, and HER2 negative breast cancer; defined as ER < 1%, progesterone receptor < 1%, and HER2 negative according to ASCO/College of American Pathologists guidelines by local testing according to institutional standards. Patients with weakly ER or progesterone receptor positive disease, defined as ER and/or progesterone receptor < 5% by IHC, are eligible, if the treating physician considers the patient not eligible for endocrine therapy
  - Have locally advanced and locally recurrent skin or subcutaneous metastases not suitable for definitive (or curative) surgical resection or radiotherapy
  - Received at least 1 and no more than 3 systemic chemotherapy regimens for metastatic breast cancer and have documented disease progression on most recent therapy
  - Willing to provide a fresh skin tumor biopsy (fixed and frozen) from a nontarget lesion

- hTMB
  - Metastatic or advanced unresectable cancer with hTMB as determined using a Clinical Laboratory Improvement Amendments validated assay (at least 16/Mb) from a recent tumor tissue or blood sample
  - Patient has failed or refused available SOC therapy specific for their tumor type.

10.1.7. [redacted]



10.1.8. Inclusion Criteria for All Patients in Parts A[redacted]

1. Agreement to provide mandatory archival/baseline biopsy. A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor;
2. For patients in Part A2 or Part B2 (for Part B2, only those patients receiving 3 mg/kg of ipilimumab), and those who agree to participate in the biomarker analysis and who have a tumor site that is safe to biopsy, patients must have a biopsy within 90 days of study entry and be willing to undergo at least 1 on-treatment tumor biopsy;
3. Patients with treated brain metastases are eligible if the brain metastases are stable and the patient does not require radiation therapy or steroids. Active screening for brain metastases (e.g., brain computed tomography [CT] or magnetic resonance imaging [MRI]) is not required;
4. At least 18 years of age;
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
6. Anticipated life expectancy of at least 3 months;
7. Screening laboratory values must meet the following criteria:
   - White blood cells > 2000/μL or 2.0×10^9/L;
   - Neutrophils ≥ 1500/μL or 1.5×10^9/L;
   - Platelets ≥ 100×10^3/μL or 100×10^9/L;
   - Hemoglobin ≥ 9.0 g/dL (may have been transfused) or 90.0 g/L;
   - Creatinine ≤ 2 mg/dL or 176.8 μmol/L;
   - AST ≤ 2.5 × upper limit of normal (ULN); ≤ 5 × ULN for patients with liver metastasis; < 3 × ULN for patients in Part C (vemurafenib + CX-072). No upper limit for patients with hepatocellular carcinoma (HCC) or pancreatic cancer;
   - ALT ≤ 2.5 × ULN; ≤ 5 × ULN for patients with liver metastasis; < 3 × ULN for patients in Part C (vemurafenib + CX-072). No ULN for patients with HCC or pancreatic cancer;
   - Total bilirubin within ULN (unless diagnosed with Gilbert's syndrome, those patients must have a total bilirubin < 3.0 mg/dL or 51.3 μmol/L). No upper limit for patients with HCC; and
   - Amylase and lipase ≤ 1.5 × ULN. No upper limit for patients with pancreatic cancer;

8. Women of childbearing potential and males must agree to use a highly effective method of contraception (details provided in APPENDIX 5) prior to study entry, while on study drug, and for a period of 105 days following the last treatment and for 180 days if receiving vemurafenib;

- Highly effective methods of contraception which result in a low failure rate (i.e., < 1% per year) when used consistently and correctly include implants, injectables, combined hormonal contraceptives, some intrauterine devices, sexual abstinence, or a vasectomized partner;
    - Combined hormonal contraceptives are not a highly effective method of contraception for patients taking vemurafenib in Part C; and
    - True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception); and

9. The ability to understand and the willingness to sign a written ICF and adhere to study schedule and prohibitions.

10.2. Exclusion Criteria

Patients who fulfill any of the following criteria at screening will not be eligible for admission into the study.

1. Prior therapy with a chimeric antigen receptor (CAR) T-cell containing regimen;
2. Baseline QTc is > 470 ms or taking any medication known to prolong the QT interval;
3. Prior history of myocarditis irrespective of the cause;
4. Treatment with strong cytochrome P450 (CYP) 3A4 inhibitors or inducers, as well as use of CYP1A2 substrates with a narrow therapeutic window assigned to the vemurafenib treatment arm. http://medicine.iupui.edu/clinpharm/ddis/main-table/;
5. History of severe allergic or anaphylactic reactions to human mAb therapy or known hypersensitivity to any Probody therapeutic;
6. Active or history of uveal, mucosal, or ocular melanoma is excluded in Parts B2 and C;
7. History of interstitial lung disease for patients with TET;

- Patients with TET are excluded in Parts B1 and B2;

8. Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)-related illness, acute or chronic hepatitis B or C; patients with HIV that have an undetectable viral load and a CD4 cell count > 400/mL and who remain on antiretroviral regimen will be eligible for enrollment into anal SCC cohorts in Parts D and E and hTMB cohort in Part D;

9. History of or current active autoimmune diseases, including but not limited to inflammatory bowel diseases, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, systemic sclerosis, systemic lupus erythematosus, autoimmune vasculitis, autoimmune neuropathies, type 1 insulin dependent diabetes mellitus, or myasthenia gravis;
10. History of syndrome or medical condition(s) that requires systemic steroids (> 10 mg daily prednisone equivalents) or immunosuppressive medications;
11. History of allogeneic tissue/solid organ transplant, prior stem cell or bone marrow transplant;
12. Chemotherapy, biochemotherapy, or immunotherapy or any investigational treatment within 14 days prior to receiving any study drug; radiation therapy within 3 months prior to receiving study medication (except for radiotherapy for the purposes of palliation confined to a single field that is not the target lesion);
13. Patients in Part C cannot have a glomerular filtration rate < 60 mL/min/1.73 m^2;
14. Major surgery (requiring general anesthesia) within 3 months or minor surgery (excluding biopsies conducted with local/topical anesthesia) or gamma knife treatment within 14 days (with adequate healing) of administration of any study drug;
15. Unresolved acute toxicity of the NCI CTCAE v4.03 Grade > 1 (or baseline, whichever is greater) that may put the patient at high risk under the current treatment. Alopecia and other nonacute toxicities are acceptable;
16. History of malignancy that is active within the previous 2 years except for localized cancers that are not related to the current cancer being treated and considered to have been cured and, in the opinion of the Investigator, present a low risk for recurrence. These exceptions include, but are not limited to, basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix or breast;
17. Received a live vaccine within 30 days prior to first dose of study drug;
18. Known pre-existing condition of age-related macular degeneration;
19. Intercurrent illness, including, but not limited to, symptomatic congestive heart failure (i.e., New York Heart Association Class III or IV), unstable angina pectoris, clinically significant and uncontrolled cardiac arrhythmia, nonhealing wound or ulcer, or psychiatric illness/social situations that would limit compliance with study requirements;
20. Pleural effusion, pericardial effusion, or recurrent ascites drainage;
21. Ongoing or active infection (including fever within 48 hours of screening);
22. Participating in an ongoing clinical study involving treatment with medications, radiation, or surgery; or
23. Women who are pregnant or breastfeeding.

11. INVESTIGATIONAL PRODUCT

11.1. Identity of Investigational Product

CX-072 is an anti–PD-L1-targeted, recombinant, protease-activatable antibody prodrug (Probody therapeutic).

Diluent for CX-072 is a sterile solution provided specifically for use with CX-072 IP for dose preparation for the first 2 dose levels.

11.2. Identity of Reference Therapy

11.2.1. Yervoy (Ipilimumab)

Yervoy is a human CTLA-4 blocking antibody indicated for the treatment of unresectable or metastatic melanoma. Yervoy is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution for IV infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL.

11.2.2. Zelboraf® (Vemurafenib)

Zelboraf is a kinase inhibitor indicated for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation as detected by an approved test. It is available as 240 mg tablets for oral use. Tablets are white to off-white and are supplied as 240 mg film-coated tablets with VEM debossed on 1 side.

11.3. Packaging and Labeling of Clinical Supplies

CX-072 is supplied as a sterile, preservative-free solution in [redacted] at a concentration of [redacted] The label for CX-072 will include standard product information. It will also include "CAUTION: New Drug – Limited by United States Law to Investigational Use."

Diluent for CX-072 is supplied as a sterile, preservative-free solution in [redacted] vials. The label for Diluent for CX-072 will include standard product information. It will also include "CAUTION: New Drug – Limited by United States Law to Investigational Use."

Ipilimumab is supplied in single-use vials of 50 mg (5 mg/mL) and 200 mg (5 mg/mL).

Vemurafenib is supplied as a 240 mg tablet in bottles of 120 or 112 tablets for US sites or as a 240 mg tablet in aluminum perforated unit dose blisters in packs of 56 × 1 tablet (7 blisters of 8 × 1 tablet per carton) for rest of the world sites. The primary packaging will remain unchanged.

11.4. Storage of Clinical Supplies

[redacted]

[redacted]

Diluent for CX-072: Diluent vials must be stored at a temperature of 2°C to 8°C (36°F to 46°F). Vials should be stored in the carton. Recommended safety measures for preparation and handling of Diluent for CX-072 include laboratory coats and gloves. Do not freeze.

Ipilimumab: Store under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials from light.

Vemurafenib: Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Store in the original container with the lid tightly closed.

It is the responsibility of the Investigator to ensure that the IP and reference therapy is stored as specified by the Sponsor and in accordance with applicable regulatory requirements.

11.5. Dosage, Study Drug Preparation, and Administration

11.5.1. CX-072

Dosage

In the dose escalation portion of the study, CX-072 is administered by IV at a dose of 0.03, 0.1, 0.3, 1, 3, 10, and 30 mg/kg per dose q2wk or q3wk. In Part D and the Part A, imaging substudy CX-072 is administered by IV at a dose of 10 mg/kg q2wk. [redacted]

Part A (monotherapy dose escalation) of the study permitted escalation up to 30 mg/kg of CX-072. Three patients were enrolled and dosed in the 30 mg/kg cohort and while none of the patients had a DLT during the DLT period, 1 patient had a Grade 4 elevation of ALT and a Grade 3 elevation of AST detected at Cycle 1 Day 42. CX-072 was discontinued, and the levels resolved with administration of steroids. This event was assessed by the Investigator and the Sponsor as related to CX-072. CytomX terminated further evaluation of any dosing at 30 mg/kg of CX-072 in monotherapy and combination. Therefore, cohorts in Parts B and C that called for combinations with CX-072 at 30 mg/kg will not be explored.

Study Drug Preparation

[redacted]

Study Drug Administration

Treatment will be administered on an outpatient basis, with inpatient admission as needed for any treatment or monitoring outside of clinic hours or for management of significant acute toxicity.

All infusions will be administered through a nonpyrogenic, low protein binding in-line filter (pore size of 0.2 μm). Following completion of the infusion, flush with an adequate amount of normal saline for infusion.

Do not co-administer other drugs concurrently through the same IV line.

CX-072 should be administered under the supervision of a physician or other study personnel experienced in the use of IV agents.

[redacted]

Additional information on study drug preparation can be found in the Pharmacy Manual.

11.5.1.1. Product complaints

A product complaint is any perceived deficiency related to physical, chemical, or biological properties or the labeling or packaging of a product.

If the solution is cloudy, is discolored, or contains extraneous particulate matter, quarantine the product and report the deficiency on a Product Complaint Form as described in the Pharmacy Manual. A complaint Investigator will follow-up to obtain additional information and provide instructions on how to return the product.

Record the product return on the Drug Accountability Log to ensure complete tracking of drug supply.

11.5.2. Yervoy (Ipilimumab)

Ipilimumab is supplied as a sterile, preservative-free solution in 10 mL (50 mg) and 40 mL (200 mg) vials at a concentration of 5 mg/mL. Dosing will be based on the patient's weight and dose level assignment. Ipilimumab may be diluted with 0.9% sodium chloride injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to a final concentration ranging from 1 to 2 mg/mL. Follow the package insert for detailed information.

[redacted]

11.5.3. Zelboraf (Vemurafenib)

Vemurafenib will be supplied in oral tablet form. Vemurafenib 960 mg will be administered in PO form twice daily (approximately q12h) with or without a meal.

Patient compliance with vemurafenib dosing will be assessed throughout the study via pill counts and/or patient diary.

11.6. Management of Infusion Reactions

Pre-medication

Patients will not be pre-medicated prior to the CX-072 infusion, unless the Sponsor determines that pre-medication is warranted.

Patients must not receive any pre-medications prior to infusions, unless it is determined during the course of the study that the occurrence of infusion-related reactions (IRRs) warrants routine prophylactic treatment. Thereafter, patients may receive pre-medication with 650 to 1000 mg PO acetaminophen and/or histamine antagonists (e.g., diphenhydramine and/or ranitidine 50 mg IV each) at the discretion of the Investigator. Pre-medication with corticosteroids should not routinely be used, unless IRRs are experienced with a previous dose that required corticosteroid treatment, or it is later determined during the study by the Medical Monitor and Investigators that it would be in the best interest of patients to pre-medicate all patients with corticosteroids.

For allergic (hypersensitivity) reactions occurring during or after study drug administration, follow the guidelines listed in Table 10.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

Table 10: Management of Allergic Reactions

Grade of Allergic Reaction	Treatment
Grade 1: Transient flushing or rash, drug fever < 38°C (< 100.4°F).	Remain at bedside and monitor patient until recovery from symptoms.
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hours.	Stop the CX-072 infusion, begin an IV infusion of normal saline and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325-1000 mg PO; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then the infusion should be discontinued and no further CX-072 will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the patient until resolution of symptoms. Pre-medication will be instituted in patients who experience an allergic reaction to IP.
Grade 3: Prolonged (e.g., > 6 hours, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates).	Immediately discontinue infusion of CX-072. Begin an IV infusion of normal saline, and treat the patient as follows: • Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. •CX-072 will be permanently discontinued for **prolonged** Grade 3 allergic reaction, unless continuation of therapy is believed to provide potential clinical benefit and no other reasonable alternatives exist, then re-challenge may be pursued at the discretion of the Investigator after consultation with the Medical Monitor.
Grade 4: Life-threatening consequences; urgent intervention indicated.	Follow treatment for Grade 3 allergic reaction and monitor patient until recovery from symptoms. CX-072 will be **permanently discontinued**.
AE = adverse event; IP = investigational product; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = oral.	

During an infusion reaction, vital signs will be obtained every 2 to 5 minutes until stable. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

12. DOSE MODIFICATIONS OR MISSED DOSES

There must be a minimum of 14 days between study drug infusions. In exceptional circumstances, an infusion may be delayed for up to 7 days. Infusions that cannot be administered in that time frame will be considered a missed dose and the patient should come in for their next, regularly scheduled visit, relative to Day 1. A patient will be considered to have discontinued study drug if he/she misses 4 consecutive doses.[1]

12.1. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will monitor the safety of the study for Parts A[redacted]. The DSMB will consist of individuals in relevant fields of expertise. It will convene on a regular basis (at least 2 times per year) and will review all safety and efficacy information to determine whether the study should continue unchanged or whether protocol modifications are required to ensure patient safety. Details on the DSMB are provided in APPENDIX 3 and in a separate DSMB charter. The DSMB will make recommendations to the Sponsor, who will make ultimate decisions regarding study alteration or discontinuation.

12.1.1. Dose Modifications for CX-072 Adverse Events

The following guidance is for dose modification of CX-072 and also addresses conditions outside of their respective labels in which ipilimumab or vemurafenib dosing would be reduced or discontinued.

Dose reduction of CX-072 is not permitted. Delays or permanent discontinuation of CX-072 may be required as dictated in Table 11.

[1] For patients who are responding to treatment, the Medical Monitor should be notified to discuss the treatment delay and whether study drug may be re-started.

Table 11: Dose Modifications for CX-072

Adverse Event	Withhold CX-072	Permanently Discontinue CX-072
Pneumonitis	Grade 2	Grade 3 or 4
Colitis	Grade 2 or 3	Grade 4
AST or ALT	> 3 and up to 5 × ULN	> 5 × ULN
Total bilirubin	> 1.5 and up to 3 × ULN	> 3 × ULN
Creatinine	> 1.5 and up to 6 × ULN or greater than 1.5 × baseline	> 6 × ULN
Hypophysitis	Symptomatic	--
Myocarditis	Any	--
Ocular inflammatory toxicity	Grade 2	Grade 3 or 4
Hyperthyroidism	Grade 3	--
Any other severe or Grade 3 treatment-related adverse reaction	Withhold[1]	Any severe or Grade 3 treatment-related AE that recurs; Grade 4
Life-threatening or Grade 4 adverse reaction	--	Permanently discontinue
Grade 3 or 4 immune-related adverse reaction	Grade 3 Withhold and contact Sponsor's Medical Monitor to discuss treatment, which may include administration of systemic steroids	Grade 4 Permanently discontinue and contact Sponsor's Medical Monitor to discuss treatment, which may include administration of systemic steroids

[1]Excluding amylase or lipase elevations.
This table is general guidance. If a laboratory value is elevated at baseline, the Medical Monitor should be contacted for dosing adjustments.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Resume CX-072 in patients whose adverse reactions recover to Grade 0 to 1 within 2 weeks or at the discretion of the Investigator.

In the event of a major surgery (biopsy excluded) the patient should be discontinued from the study.

CX-072 should be permanently discontinued for any of the following:

- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiation, or
- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 1 or resolve within 12 weeks after the last dose of CX-072.

Additional guidelines for the management of AEs follow:

Immune-mediated pneumonitis

Monitor patients for signs and symptoms of pneumonitis. For ≥ Grade 2 pneumonitis, recommend treatment with corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents, followed by a corticosteroid taper. Withhold CX-072 for Grade 2 immune-mediated pneumonitis and permanently discontinue treatment for Grade 3 or 4 or recurrent pneumonitis upon restarting CX-072.

Immune-mediated colitis

For severe (Grade 3) or life-threatening (Grade 4) colitis, administer corticosteroids at a dose of 1.5 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper. For moderate (Grade 2) colitis of > 5 days in duration, administer corticosteroids at 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. For Grade 2 colitis that worsens or does not improve after initiation of corticosteroids, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. Withhold CX-072 for Grade 2 or 3 immune-mediated colitis and permanently discontinue treatment for Grade 4 or recurrent colitis upon restarting CX-072.

Immune-mediated hepatitis

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold CX-072 for Grade 2 and permanently discontinue for Grade 3 or Grade 4 immune-mediated hepatitis.

Immune-mediated hypothyroidism and hyperthyroidism

Monitor thyroid function prior to and periodically (every 3 months and as clinically indicated) during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of CX-072 for hypothyroidism or hyperthyroidism.

Myocarditis

Monitor patients for myocarditis prior to and periodically during treatment. In case of newly occurring signs of arrhythmia, discontinue CX-072 and ipilimumab until myocarditis and/or acute heart failure is ruled out.

Other immune-mediated adverse reactions

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold CX-072, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvements to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting CX-072 after completion of corticosteroid taper based on the severity of the event.

Refinement of the recommended treatment of CX-072–related AEs will be made as the study progresses.

If any of the immune-related symptoms worsen or do not improve with the guidelines above, tumor necrosis factor-α inhibitors may be administered at the discretion of the Investigator.

12.1.2. Special Instructions Regarding Dose Modification of Ipilimumab or Vemurafenib

For dose modification of ipilimumab and vemurafenib, the Investigator is directed to the respective package inserts.

- Ipilimumab: Yervoy US Package Insert, 2015; and
- Vemurafenib: Zelboraf US Package Insert, 2016.

See Section 12.1.1 for dose modification of CX-072 and conditions outside of their respective labels in which ipilimumab or vemurafenib dosing would be reduced or discontinued.

If CX-072 is discontinued, ipilimumab or vemurafenib, as applicable, will also be discontinued. Delays in CX-072 treatment will also result in a delay of ipilimumab or vemurafenib, until a maximum of 4 doses of ipilimumab have been administered.

CX-072 treatment may continue in the event of a noninflammatory event that, in the judgment of the Investigator, is due to vemurafenib. However, in the event that the event does not improve after vemurafenib dosing adjustments, CX-072 will be adjusted as per the protocol.

Additional modifications of ipilimumab and vemurafenib may be performed at the discretion of the Investigator after discussion with the Medical Monitor.

13. PRIOR AND CONCOMITANT MEDICATIONS

All medications taken within 30 days before the administration of study drug and all concomitant medications and therapies administered during the study will be recorded on the relevant electronic case report form (eCRF).

1. Patients enrolled to the CX-072/vemurafenib arm of the study should avoid concomitant administration of vemurafenib with strong CYP3A4 inhibitors or inducers, as well as concomitant use with CYP1A2 substrates with a narrow therapeutic window. Patients taking concomitant moderate CYP inhibitors or inducers during the study should be monitored for possible complications (P450 Drug Interaction Table 2015);
2. Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the patient is on a stable dose. Nonabsorbed intra-articular steroid injections will be permitted. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration (if authorized by the study physician). The use of steroids as prophylactic treatment for patients with contrast allergies to diagnostic imaging contrast dyes will be permitted;
3. The use of herbal remedies (herbal preparation in the Chinese traditional medicine), other marketed anti-cancer chemo/immunotherapy/hormonal drugs, or investigational drugs is not permitted;
4. New chemotherapy, hormonal (exception allowed for prostate cancer patients receiving androgen deprivation therapy or pre-menopausal women receiving gonadotropin-releasing hormone [GnRH] agonists), radiation or immunotherapy is not permitted during the screening or treatment periods;
5. Palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracentesis or paracentesis for comfort) are permitted after consultation with the Medical Monitor;
6. The use of live vaccines while on study drug is prohibited. The use of any killed or attenuated vaccines for the prevention of influenza is permitted. The use of other killed or attenuated vaccines for the prevention of infectious diseases may be permitted on a case-by-case basis after discussion with the Medical Monitor. Any vaccinations administered during the study must be documented on the patient's records and in the eCRF; and
7. Co-administration of bisphosphonates and denosumab is permitted for patients being administered bisphosphonates and denosumab prior to the study. These drugs should be continued at the same dose during the study.

All concomitant medications taken by the patient while in the study should be recorded in the eCRF. Once a patient enters the follow-up period, only new therapies for the treatment of their cancer should be recorded in the eCRF.

14. PHAMACOKINETIC, IMMUNOGENICITY, AND EXPLORATORY BIOMARKER ASSESSMENTS

14.1. Pharmacokinetic Assessments

Concentration versus time data will be tabulated and plotted for the individual and mean serum total and intact CX-072 moieties. PK parameters including AUC, C_{max}, time to reach C_{max}, C_{min}, clearance, and volume of distribution at steady state will be calculated for total and intact CX-072 moieties as appropriate and as data allow. Additional parameters such as $t_{1/2}$ and accumulation may be calculated, and dose proportionality will be assessed. Estimates for these parameters will be tabulated and summarized (e.g., mean, standard deviation, and coefficient of variation).

Vemurafenib C_{max} and C_{min} and ipilimumab C_{max} and C_{min} will be summarized using descriptive statistics.

14.1.1. Pharmacokinetics Collection

Samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. Times noted are post end of infusion (EOI). The full schedule of PK blood sampling can be found in Table 17.

The date and time of each dose administered and the times at which PK samples are collected should be recorded in the eCRF. If the infusion was interrupted, the reason for interruption will also be documented in the eCRF and a sample will be collected at the end of the infusion and at the times specified after the EOI.

14.2. Immunogenicity Assessments

Serum samples will be collected from study participants, as described in Table 12, Table 13, Table 14, and Table 15 to assess the immunogenicity of CX-072 and ipilimumab (when ipilimumab is administered). Samples will be initially screened for ADA to CX-072 and ipilimumab (when ipilimumab is administered). If the sample is found to be ADA positive in the screening assay, a confirmatory assay and a titer assay will be performed to further characterize ADAs. Incidence of ADA response and the potential correlation with PK, PD, and safety parameters may be assessed.

14.2.1. Immunogenicity Collection

The full schedule of ADA blood sampling can be found in Table 12, Table 13, Table 14, and Table 15.

15. STUDY PROCEDURES AND SCHEDULE OF EVENTS

The study procedures to be followed are outlined in the Schedules of Events. Refer to the Common Core Document for a description of each procedure.

Table 12: Schedule of Events: Parts A and D: CX-072 Monotherapy and Part C: CX-072 Plus Vemurafenib

Period/Procedure	Screening Period	Treatment Period												
		Cycle 1 ± 2 days of scheduled visit							Cycles 2 – n ± 2 days of scheduled visit					EOT
Study/Visit Day[1]	**-30 to 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 56**[2]	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 56**[2]	
Informed Consent	X													
Medical History[3]	X													
Prior Treatment/Therapies for Cancer	X													
Demographics	X													
AE Assessment[4]		X			X	X	X		X	X	X	X		X
Concomitant Medications[4]	X	X			X	X	X		X	X	X	X		X
Limited Resource Utilization		X			X	X	X		X	X	X	X		X
Study Drug Administration														
CX-072 Infusion[5]		X			X	X	X		X	X	X	X		
Vemurafenib Oral Tablets[6]		960 mg twice daily approximately 12 hours apart												
Imaging														
CT/MRI (chest, abdomen, pelvis)[7]	X	Every 8 weeks for 12 months then every 12 weeks												X
PET/CT or PET with Diagnostic CT[8]	X	Every 8 weeks for 12 months then every 12 weeks												X
Bone Scan[9]	X	Every 8 weeks for 12 months then every 12 weeks												X
ECG[10]	X	X			X[11]	X[11]			X[11]		X[11]			X[11]
Clinical Procedures														
Physical Examination[12]	X	X			X	X	X		X	X	X	X		X
Vital Signs[13]	X	X			X	X	X		X	X	X	X		X
ECOG Performance Status[14]	X	X			X	X	X		X	X	X	X		X
Height[13]	X													
Weight[13]	X	X			X	X	X		X	X	X	X		

Table 12: Schedule of Events: Parts A and D: CX-072 Monotherapy and Part C: CX-072 Plus Vemurafenib (Continued)

Period/Procedure	Screening Period	Treatment Period												
		Cycle 1 ± 2 days of scheduled visit							Cycles 2 – n ± 2 days of scheduled visit					EOT
Study/Visit Day[1]	**-30 to 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 56[2]**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 56[2]**	
B Symptoms[15]	X	X			X	X	X		X	X	X	X		
Diagnosis Confirmation, Stage and Baseline Disease Assessment and Documentation[16]	X													
Tumor Response Assessment[16]	X	Every 8 weeks for 12 months then every 12 weeks												X
Laboratory Assessments														
ACTH	X													
Hematology[17]	X	X			X	X	X		X	X	X	X		X
Serum Chemistry[18]	X	X			X	X	X		X	X	X	X		X
Thyroid Function[19]		X	Every 3 months											X
HIV, Hepatitis B and C[20]	X													
Coagulation[21]	X	X												X
Urinalysis[22]	X	X							X					X
Pregnancy Test[23]	X	X				X			X		X			X
Archival/Baseline Biopsy[24]	X													
[redacted]														
Sample for PK		PK samples for CX-072 will be collected for Parts A, C, and D according to Table 17. PK will be collected for vemurafenib according to Table 17.												
Serum sample for ADA[27]		X				X			X		X			X
Blood sample for tumor mutation burden[28]	X													
Blood sample for TET safety monitoring[29]	X	X			X	X	X		X	X	X	X		X
Blood sample for CEA and CA 19-1[30]	X	Every 8 weeks for 12 months then every 12 weeks												X

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CBC = complete blood count; CEA = carcinoembryonic antigen; CRC = colorectal cancer; CT = computed tomography; CV = cardiovascular; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOS = end of study; EOT = end of treatment; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; hTMB = high tumor mutational burden; INR = international normalized ratio; IP = investigational product; IV = intravenous; LDH = lactate dehydrogenase; mCRPC = metastatic castration-resistant prostate cancer; MEL = melanoma; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; qXwk = every X weeks; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TET = thymic epithelial tumor; TNBC = triple negative breast cancer; TSH = thyroid-stimulating hormone.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (e.g., weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit. Visits conducted outside the windows are to be discussed with the Medical Monitor in advance.
2. This is not a clinic visit; this is for radiologic assessment and response assessment by the Investigator prior to beginning the next cycle of treatment. These assessments should occur between -3 days and the indicated day, and before administering the first dose of the next cycle of treatment.
3. To include confirmation of previous cancer diagnosis and recording cancer treatment history, current symptoms at baseline (defined as value at screening), and medications currently being taken.
4. Adverse events and concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Once study drug is discontinued, only new medications for the treatment of the patient's cancer need to be recorded, as applicable during follow-up.
5. If a ≥ Grade 2 infusion-related reaction is observed during or after an infusion, a local blood draw is required to measure tryptase, total immunoglobulin E, and complement C3a and C5 preferably within 2 hours and no more than 6 hours after the first signs/symptoms of the reaction.
6. Only administered in Part C CX-072 + vemurafenib.
7. CT and/or MRI to be performed within 30 days prior to the first dose of CX-072 and repeated q8wk (Day 0 to 12 months) and then q12wk (Month 13 to 24). Scans will also be repeated at the EOT visit and, if applicable, at the EOS visit (i.e., if the patient has not experienced progression). Methodology used should remain consistent for the duration of patient participation in the study.
8. Lymphoma patients only. Methodology used to evaluate lesions should remain consistent for the duration of patient participation in the study.
9. Bone scans must be done at all visits indicated for patients with mCRPC. For patients with MEL, RCC, CRC, and NSCLC, perform bone scan at baseline (defined as value at screening) or at response assessment visits as clinically indicated. Collect and hold scans for review by an independent committee.
10. 12-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible) and archived, while supine at screening, at defined time points, at the EOT visit, and as clinically indicated.
11. For patients in Part A: perform ECG at screening, 30 (± 15) minutes before and after CX-072 infusions on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 2 Day 29, and at the EOT visit. For patients in Part C: perform ECG at screening, 30 (± 15) minutes before and after CX-072 infusions on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 1 Day 29, Cycle 2 Day 1, Cycle 2 Day 29, and again every 2 cycles thereafter, or more often as clinically indicated, and at the EOT visit. For patients in Part D: perform ECG at screening, 30 (± 15) minutes before and after CX-072 infusions on Cycle 1 Day 1, Cycle 2 Day 29, and at the EOT visit.
12. Physical examinations should be performed at screening and on Day 1, on each day of Probody therapeutic dosing, and at the EOT visit. At all other visits, targeted physical examinations should be performed as needed by patient symptoms or clinical observations, focused on key organ systems of interest (e.g., CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings). Dermatologic evaluations should be performed prior to initiation of therapy and every 2 months while on therapy. Dermatologic monitoring for 6 months following discontinuation of vemurafenib is recommended.
13. Vital signs include heart rate and blood pressure (supine), temperature, respiratory rate, and pulse oximetry. During the first 4 doses of IP, vital signs should be measured within 60 (± 5) minutes prior to infusion, every 15 (± 5) minutes during infusion, at the EOI (± 5 minutes), and approximately hourly for 4 hours (± 5 minutes) after the completion of infusion. On all other infusion days, vital signs should be measured within 60 (± 5) minutes prior to infusion, at the EOI (± 5 minutes), and 60 (± 5) minutes after completion of infusion (unless clinical signs require more frequent monitoring). For CX-072 doses administered via IV push, vital signs will be measured pre-dose (± 5 minutes), at the end of the injection (± 5 minutes), and then as per the schedule above. Weight should be measured at screening and before each dose. Height should be measured at screening only. During an infusion reaction, vital signs should be recorded every 2 to 5 minutes until stable.
14. Performance status should be assessed at screening, Day 1 and prior to each subsequent infusion, and at EOT visit.
15. Lymphoma patients only, B symptoms: fever, chills, fatigue, night sweats, weight loss, and pruritus.
16. Tumor measurements will be recorded at baseline (defined as value at screening) and repeated q8wk (from Dose 1 for 12 months), then q12wk until EOT and at the EOT visit; refer to tumor-specific response criteria guidelines in the Common Core Document. The patient will be re-baselined at the initial/unconfirmed progression. For TNBC patients with skin lesions, skin lesions must be photographed along with a ruler at all time points for tumor assessments. Methodology used for tumor assessments should remain consistent for the duration of patient participation in the study.

17. Including CBC with differential, including blast count, platelet count pre-dose.
18. Including alkaline phosphatase, AST/SGOT and ALT/SGPT, amylase, lipase, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, magnesium, and LDH. Blood glucose should be fasting to evaluate possible hyperglycemia. Calculated creatinine clearance is required at screening. Laboratory assessments drawn on the day of infusion should be drawn pre-dose.
19. Including TSH, free T4 and T3. Thyroid function will be assessed at baseline (defined as value at Cycle 1 Day 1), every 3 months during treatment, at the discretion of the Investigator, and at the EOT visit.
20. HIV positive patients in Part D anal SCC and hTMB cohorts need to have their CD4 count and viral load captured at screening to ensure eligibility criteria have been met.
21. Including PT/aPTT/INR at screening, and pre-dose Day 1, at EOT visit, and as clinically indicated.
22. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at screening, Day 1 of each cycle, and the EOT visit.
23. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at screening (if screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted). Urine pregnancy test (with serum test as needed for confirmation) should be obtained monthly (i.e., q4wk) while on treatment, and at the EOT visit.
24. Central pathology review is required for patients with TNBC with skin lesions, TET, and UPS (prior to enrollment for UPS).
[redacted]
27. ADA samples will be on Cycle 1 Day 1, Cycle 1 Day 29, Cycle 2 Day 1, Cycle 2 Day 29, Cycle 4 Day 29, and on Day 29 of every 4 cycles thereafter (e.g., Cycle 8 Day 29, Cycle 12 Day 29, etc.) prior to each CX-072 dose, at EOT, and > 90 days following EOT.
28. For patients in Part D, a 16 mL blood sample will be drawn to test for tumor mutation burden at screening.
29. For patients in Part A and Part D, all patients with TET will be screened for acetylcholine receptor autoantibodies, muscle-specific tyrosine kinase autoantibodies, and anti-skeletal muscle antibodies at screening, Cycle 1 Day 1, Cycle 1 Day 15, Cycle 1 Day 29, Cycle 1 Day 43, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 2 Day 29, Cycle 2 Day 43, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 3 Day 29, Cycle 3 Day 43, and EOT.
30. For patients in Part D with small bowel adenocarcinoma, a blood sample will be drawn at baseline and repeated q8wk (from Dose 1 for 12 months), then q12wk until EOT and at the EOT visit for measurement of CEA and CA 19-9.

Patients will be followed approximately every 3 months for progression and overall survival (± 14 days) after the last dose of IP, or until withdrawal from study participation or death, whichever occurs first. An EOT visit will be conducted at the conclusion of treatment. The initial follow-up visit should be scheduled approximately 28 days after the patient's last study drug administration. Refer to Table 16. Toxicity management may require additional visits at the discretion of the Investigator.

Table 13: Schedule of Events: Part A2: CX-072 Monotherapy

Period/Procedure	Screening Period	Treatment Period												
		Cycle 1 ± 2 days of scheduled visit							Cycles 2 – n ± 2 days of scheduled visit					EOT
Study/Visit Day[1]	**-30 to 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 56**[2]	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 56**[2]	
Informed Consent	X													
Medical History[3]	X													
Prior Treatment/Therapies for Cancer	X													
Demographics	X													
AE Assessment[4]		X			X	X	X		X	X	X	X		X
Concomitant Medications[4]	X	X			X	X	X		X	X	X	X		X
Limited Resource Utilization		X			X	X	X		X	X	X	X		X
Study Drug Administration														
CX-072 Infusion[5]		X			X	X	X		X	X	X	X		
Imaging														
CT/MRI (chest, abdomen, pelvis)[6]	X	Every 8 weeks for 12 months then every 12 weeks												X
PET/CT or PET with Diagnostic CT[7]	X	Every 8 weeks for 12 months then every 12 weeks												X
Bone Scan[8]	X	Every 8 weeks for 12 months then every 12 weeks												X
ECG[9]	X	X							X		X			X
Clinical Procedures														
Physical Examination[10]	X	X			X	X	X		X	X	X	X		X
Vital Signs[11]	X	X			X	X	X		X	X	X	X		X
ECOG Performance Status[12]	X	X			X	X	X		X	X	X	X		X
Height[11]	X													
Weight[11]	X	X			X	X	X		X	X	X	X		
B Symptoms[13]	X	X			X	X	X		X	X	X	X		

Table 13: Schedule of Events: Part A2: CX-072 Monotherapy (Continued)

Period/Procedure	Screening Period	Treatment Period												
		Cycle 1 ± 2 days of scheduled visit							Cycles 2 – n ± 2 days of scheduled visit					EOT
Study/Visit Day[1]	**-30 to 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 56[2]**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 56[2]**	
Diagnosis Confirmation, Stage and Baseline Disease Assessment and Documentation[14]	X													
Tumor Response Assessment[14]	X	Every 8 weeks for 12 months then every 12 weeks												X
Laboratory Assessments														
ACTH	X													
Hematology[15]	X	X			X	X	X		X	X	X	X		X
Serum Chemistry[16]	X	X			X	X	X		X	X	X	X		X
Thyroid Function[17]		X	Every 3 months											X
HIV, Hepatitis B and C	X													
Coagulation[18]	X	X												X
Urinalysis[19]	X	X							X					X
Pregnancy Test[20]	X	X				X			X		X			X
Archival/Baseline Biopsy	X													
[redacted]														
Sample for PK		PK samples for CX-072 will be collected for Part A2 according to Table 17.												
Serum sample for ADA[23]		X				X			X		X			X
Blood sample for TET safety monitoring[24]	X	X			X	X	X		X	X	X	X		X

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRC = colorectal cancer; CT = computed tomography; CV = cardiovascular; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOS = end of study; EOT = end of treatment; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; INR = international normalized ratio; IP = investigational product; LDH = lactate dehydrogenase; mCRPC = metastatic castration-resistant prostate cancer; MEL = melanoma; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; qXwk = every X weeks; RCC = renal cell carcinoma; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TET = thymic epithelial tumor; TSH = thyroid-stimulating hormone.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (e.g., weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit. Visits conducted outside the windows are to be discussed with the Medical Monitor in advance.
2. This is not a clinic visit; this is for radiologic assessment and response assessment by the Investigator prior to beginning the next cycle of treatment. These assessments should occur between -3 days and the indicated day, and before administering the first dose of the next cycle of treatment.
3. To include confirmation of previous cancer diagnosis and recording cancer treatment history, current symptoms at baseline (defined as value at screening), and medications currently being taken.
4. Adverse events and concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Once study drug is discontinued, only new medications for the treatment of the patient's cancer need to be recorded, as applicable during follow-up.
5. If a ≥ Grade 2 infusion-related reaction is observed during or after an infusion, a local blood draw is required to measure tryptase, total immunoglobulin E, and complement C3a and C5 preferably within 2 hours and no more than 6 hours after the first signs/symptoms of the reaction.
6. CT and/or MRI to be performed within 30 days prior to the first dose of CX-072 and repeated q8wk (Day 0 to 12 months) and then q12wk (Month 13 to 24). Scans will also be repeated at the EOT visit and, if applicable, at the EOS visit (i.e., if the patient has not experienced progression). Methodology used should remain consistent for the duration of patient participation in the study.
7. Lymphoma patients only. Methodology used to evaluate lesions should remain consistent for the duration of patient participation in the study.
8. Bone scans must be done at all visits indicated for patients with mCRPC. For patients with MEL, RCC, CRC, and NSCLC, perform bone scan at baseline (defined as value at screening) or at response assessment visits as clinically indicated. Collect and hold scans for review by an independent committee.
9. 12-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible) and archived, while supine at screening, 30 (± 15) minutes before and after CX-072 infusions on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 2 Day 29, and at the EOT visit.
10. Physical examinations should be performed at screening and on Day 1, on each day of Probody therapeutic dosing, and at the EOT visit. At all other visits, targeted physical examinations should be performed as needed by patient symptoms or clinical observations, focused on key organ systems of interest (e.g., CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings). Dermatologic evaluations should be performed prior to initiation of therapy and every 2 months while on therapy.
11. Vital signs include heart rate and blood pressure (supine), temperature, respiratory rate, and pulse oximetry. During the first 4 doses of IP, vital signs should be measured within 60 (± 5) minutes prior to infusion, every 15 (± 5) minutes during infusion, at the EOI (± 5 minutes), and approximately hourly for 4 hours (± 5 minutes) after the completion of infusion. On all other infusion days, vital signs should be measured within 60 (± 5) minutes prior to infusion, at the EOI (± 5 minutes), and 60 (± 5) minutes after completion of infusion (unless clinical signs require more frequent monitoring). Weight should be measured at screening and before each dose. Height should be measured at screening only. During an infusion reaction, vital signs should be recorded every 2 to 5 minutes until stable.
12. Performance status should be assessed at screening, Day 1 and prior to each subsequent infusion, and at EOT visit.
13. Lymphoma patients only, B symptoms: fever, chills, fatigue, night sweats, weight loss, and pruritus.
14. Tumor measurements will be recorded at baseline (defined as value at screening) and repeated q8wk (from Dose 1 for 12 months), then q12wk until EOT and at the EOT visit; refer to tumor-specific response criteria guidelines in the Common Core Document. The patient will be re-baselined at the initial/unconfirmed progression. Methodology used for tumor assessments should remain consistent for the duration of patient participation in the study.
15. Including CBC with differential, including blast count, platelet count pre-dose.
16. Including alkaline phosphatase, AST/SGOT and ALT/SGPT, amylase, lipase, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, magnesium, and LDH. Blood glucose should be fasting to evaluate possible hyperglycemia. Calculated creatinine clearance is required at screening. Laboratory assessments drawn on the day of infusion should be drawn pre-dose.
17. Including TSH, free T4 and T3. Thyroid function will be assessed at baseline (defined as value at Cycle 1 Day 1), every 3 months during treatment, at the discretion of the Investigator, and at the EOT visit.
18. Including PT/aPTT/INR at screening, and pre-dose Day 1, at EOT visit, and as clinically indicated.
19. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at screening, Day 1 of each cycle, and the EOT visit.
20. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at screening (if screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted). Urine pregnancy test (with serum test as needed for confirmation) should be obtained monthly (i.e., q4wk) while on treatment, and at the EOT visit.

[redacted]

23. ADA samples will be on Cycle 1 Day 1, Cycle 1 Day 29, Cycle 2 Day 1, Cycle 2 Day 29, Cycle 4 Day 29, and on Day 29 of every 4 cycles thereafter (e.g., Cycle 8 Day 29, Cycle 12 Day 29, etc.) prior to each CX-072 dose, at EOT, and > 90 days following EOT.

24. All patients with TET will be screened for acetylcholine receptor autoantibodies, muscle-specific tyrosine kinase autoantibodies, and anti-skeletal muscle antibodies at screening, Cycle 1 Day 1, Cycle 1 Day 15, Cycle 1 Day 29, Cycle 1 Day 43, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 2 Day 29, Cycle 2 Day 43, Cycle 3 Day 1, Cycle 3 Day 15, Cycle 3 Day 29, Cycle 3 Day 43, and EOT.

Patients will be followed approximately every 3 months for progression and overall survival (± 14 days) after the last dose of IP, or until withdrawal from study participation or death, whichever occurs first. An EOT visit will be conducted at the conclusion of treatment. The initial follow-up visit should be scheduled approximately 28 days after the patient's last study drug administration. Refer to Table 16. Toxicity management may require additional visits at the discretion of the Investigator.

Table 14: Schedule of Events: Parts B1 and B2: CX-072 Plus Ipilimumab Combination

Period/Procedure	Screening Period	Treatment Period																		
		Cycle 1[1] ± 2 days of scheduled visit							Cycle 2[1] ± 2 days of scheduled visit						Cycles 3 – n ± 2 days of scheduled visit					EOT
Study/Visit Day[2]	**-30 to 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57[3]**	**Day 64**	**Day 71**	**Day 77[4]**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 56[3]**	
Informed Consent	X																			
Medical History[5]	X																			
Prior Treatment/Therapies for Cancer	X																			
Demographics	X																			
AE Assessment[6]		X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Concomitant Medications[6]	X	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Limited Resource Utilization		X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Study Drug Administration																				
CX-072 Infusion[7]		X				X			X			X			X	X	X	X		
Ipilimumab Infusion		X				X			X			X			D/C					
Imaging																				
CT/MRI (chest, abdomen, pelvis)[8]	X	Scan every 8 weeks for 12 months and then every 12 weeks																		X
PET/CT or PET with Diagnostic CT[9]	X	Scan every 8 weeks for 12 months and then every 12 weeks																		X
Bone Scan[10]	X	Scan every 8 weeks for 12 months and then every 12 weeks																		X
ECG[11]	X	X										X								X
Clinical Procedures																				
Physical Examination[12]	X	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Vital Signs[13]	X	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
ECOG Performance Status[14]	X	X				X	X		X			X			X	X	X	X		X
Height[13]	X																			
Weight[13]	X	X				X			X			X			X	X	X	X		

Table 14: Schedule of Events: Parts B1 and B2: CX-072 Plus Ipilimumab Combination (Continued)

Period/Procedure	Screening Period	Treatment Period																		
		Cycle 1[1] ± 2 days of scheduled visit							Cycle 2[1] ± 2 days of scheduled visit						Cycles 3 – n[1] ± 2 days of scheduled visit					EOT
Study/Visit Day[2]	**-30 to 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57[3]**	**Day 64**	**Day 71**	**Day 77[4]**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 56[3]**	
B Symptoms[15]	X	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Diagnosis Confirmation, Stage and Baseline Disease Assessment and Documentation[16]	X																			
Tumor Response Assessment[16]	X	Tumor response assessment every 8 weeks for 12 months and then every 12 weeks																		X
Laboratory Assessments																				
ACTH	X																			
Hematology[17]	X	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Serum Chemistry[18]	X	X		X	X	X	X	X	X	X		X	X		X	X	X	X		X
Thyroid Function[19]		X	Every 3 months																	X
HIV, Hepatitis B and C	X																			
Coagulation[20]	X	X																		X
Urinalysis[21]	X	X							X						X					X
Pregnancy Test[22]	X	X					X				X				X		X			X
Archival/Baseline Biopsy	X																			
[redacted]																				
Sample for PK		PK samples will be collected according to Table 17.																		
Serum Sample for ADA to CX-072[25]		X				X						X			X		X			X
Serum Sample for ADA to Ipilimumab[26]		X										X								

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRC = colorectal cancer; CT = computed tomography; CV = cardiovascular; D/C = discontinue; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOS = end of study; EOT = end of treatment; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; INR = international normalized ratio; IP = investigational product; LDH = lactate dehydrogenase; mCRPC = metastatic castration-resistant prostate cancer; MEL = melanoma; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; qXwk = every X weeks; RCC = renal cell carcinoma; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

1. Cycle 1 of CX-072 plus ipilimumab combination treatment is 6 weeks, Cycle 2 of CX-072 plus ipilimumab combination treatment is 5 weeks, and Cycles 3 and beyond of CX-072 are 8 weeks.
2. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (e.g., weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit. Visits conducted outside the windows are to be discussed with the Medical Monitor in advance.
3. This is not a clinic visit; this is for radiologic assessment and response assessment by the Investigator prior to beginning the next treatment. These assessments should occur between -3 days and the indicated day, and before administering the next dose of treatment.
4. This column is intentionally left blank. There are no procedures occurring on Cycle 2 Day 77.
5. To include confirmation of previous cancer diagnosis and recording cancer treatment history, current symptoms at baseline (defined as value at screening), and medications currently being taken.
6. Adverse events and concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Once study drug is discontinued, only new medications for the treatment of the patient's cancer need to be recorded, as applicable during follow-up.
7. If a ≥ Grade 2 infusion-related reaction is observed during or after an infusion, a local blood draw is required to measure tryptase, total immunoglobulin E, and complement C3a and C5 preferably within 2 hours and no more than 6 hours after the first signs/symptoms of the reaction.
8. CT and/or MRI to be performed within 30 days prior to the first dose of CX-072 and repeated q8wk (Day 0 to 12 months) and then q12wk (Month 13 to 24). Scans will also be repeated at the EOT visit and, if applicable, at the EOS visit (i.e., if the patient has not experienced progression). Methodology used should remain consistent for the duration of patient participation in the study.
9. Lymphoma patients only. Methodology used to evaluate lesions should remain consistent for the duration of patient participation in the study.
10. Bone scans must be done at all visits indicated for patients with mCRPC. For patients with MEL, RCC, CRC, and NSCLC, perform bone scan at baseline (defined as value at screening) or at response assessment visits as clinically indicated. Collect and hold scans for review by an independent committee.
11. 12-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible), and archived, while supine at screening, 30 (± 15) minutes before and after CX-072 infusion on Cycle 1 Day 1 and Cycle 2 Day 64, and again at EOT, and as clinically indicated.
12. Physical examinations should be performed at screening and on Day 1, on each day of Probody therapeutic dosing and at the EOT visit. At all other visits, targeted physical examinations should be performed as needed by patient symptoms or clinical observations, focused on key organ systems of interest (e.g., CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings). Dermatologic evaluations should be performed prior to initiation of therapy and every 2 months while on therapy.
13. Vital signs include heart rate and blood pressure (supine), temperature, respiratory rate, and pulse oximetry. During the first 4 doses of combination therapy, vital signs should be measured within 60 (± 5) minutes prior to infusion, every 15 (± 5) minutes during infusion, at the EOI (± 5 minutes), and approximately hourly for 4 hours (± 5 minutes) after the completion of infusion. On all other infusion days, vital signs should be measured within 60 (± 5) minutes prior to infusion, at the EOI (± 5 minutes), and 60 (± 5) minutes after completion of infusion (unless clinical signs require more frequent monitoring). Weight should be measured at screening and before each dose. Height should be measured at screening only. During an infusion reaction, vital signs should be recorded every 2 to 5 minutes until stable.
14. Performance status should be assessed at screening, Day 1 and prior to each subsequent infusion, Day 29, and at the EOT visit.
15. Lymphoma patients only, B symptoms: fever, chills, fatigue, night sweats, weight loss, and pruritus.
16. Tumor measurements will be recorded at baseline (defined as value at screening) and repeated q8wk (from Dose 1 for 12 months), then q12wk until EOT, and at the EOT visit; refer to tumor-specific response criteria guidelines in the Common Core Document. The patient will be re-baselined at the initial/unconfirmed progression. Methodology used for tumor assessments should remain consistent for the duration of patient participation in the study.
17. Including CBC with differential, including blast count and platelet count pre-dose.
18. Including alkaline phosphatase, AST/SGOT and ALT/SGPT, amylase, lipase, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, magnesium, and LDH. Blood glucose should be fasting to evaluate possible hyperglycemia. Calculated creatinine clearance is required at screening. Laboratory assessments drawn on the day of infusion should be drawn pre-dose.
19. Including TSH, free T4 and T3. Thyroid function will be assessed at baseline (defined as value at Cycle 1 Day 1), every 3 months during treatment, at the discretion of the Investigator, and at the EOT visit.

20. Including PT/aPTT/INR at screening, and pre-dose Day 1, at EOT visit, and as clinically indicated.
21. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at screening, Day 1 of each cycle and the EOT visit.
22. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at screening (if screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted). Urine pregnancy test (with serum test as needed for confirmation) should be obtained monthly (i.e., q4wk) while on treatment, and at EOT visit.
[redacted]
25. ADA to CX-072 samples will be on Cycle 1 Day 1, Cycle 1 Day 22, Cycle 2 Day 64, Cycle 3 Day 1, Cycle 4 Day 29, and on Day 29 of every 4 cycles thereafter (e.g., Cycle 8 Day 29, Cycle 12 Day 29, etc.) prior to each CX-072 dose, at EOT, and > 90 days following EOT.
26. ADA to ipilimumab samples will be on Cycle 1 Day 1 and Cycle 2 Day 64 prior to the ipilimumab dose.

Patients will be followed approximately every 3 months for progression and overall survival (± 14 days) after the last dose of IP, or until withdrawal from study participation or death, whichever occurs first. An EOT visit will be conducted at the conclusion of treatment. The initial follow-up visit should be scheduled approximately 28 days after the patient's last study drug administration. Refer to Table 16. Toxicity management may require additional visits at the discretion of the Investigator.

[redacted]

[redacted]

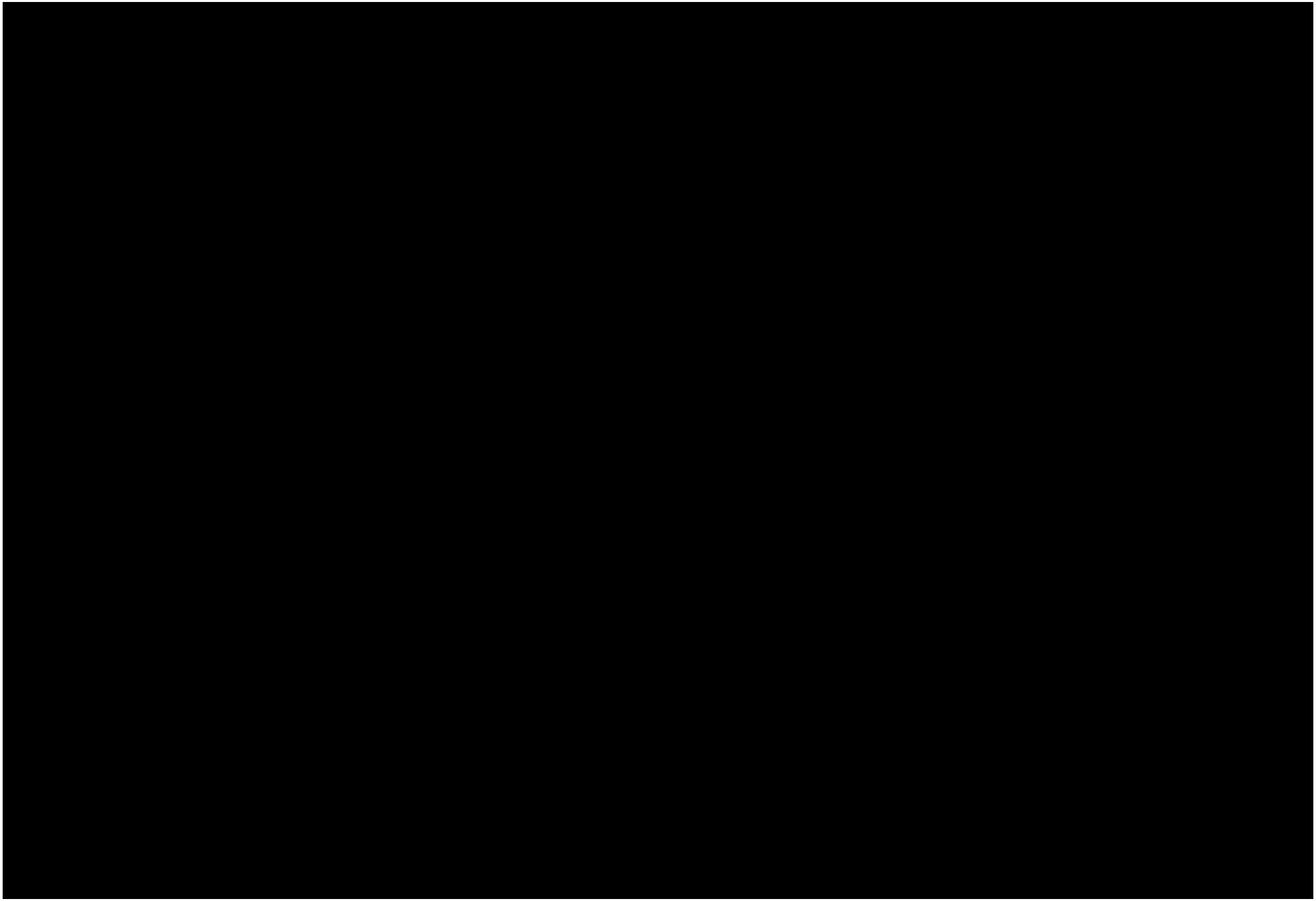


Table 16: Schedule of Events: Follow-Up Period for Parts A[redacted] of the Study

Follow-Up Period			
	Follow-Up	**Follow-Up**	**End of Study (withdraw consent/death)**
	+ 28 days	**Every 3 months**	
AE Assessment[1]	X	X	X
CT/MRI (chest, abdomen, pelvis)	X	X[2]	
PET/CT or PET with Diagnostic CT[3]	X	X[2]	
Bone Scan[4]	X	X[2]	
Physical Examination	X		
Vital Signs	X		
ECOG Performance Status	X		
Tumor Response Assessment	X	X[2]	X
Hematology	X		
Serum Chemistry	X		
Pregnancy Test		X[5]	
Survival Status	X	X	X
New Cancer Treatments[6]	X	X	X

1. For follow-up visits beyond 28 days post study drug, only serious study drug-related events and any late onset irAEs should be reported.
2. Patients with SD, PR, or CR will have imaging and tumor response assessment completed every 8 weeks for the first 12 months and then every 12 weeks until confirmed progression of disease.
3. Lymphoma patients only. Methodology used to evaluate lesions should remain consistent for the duration of patient participation in the study.
4. Bone scans must be done at all visits indicated for patients with mCRPC. For patients with MEL, RCC, CRC, and NSCLC, perform bone scan at baseline (defined as value at screening) or at response assessment visits as clinically indicated. Collect and hold scans for review by an independent committee.
5. Urine or serum pregnancy test should be obtained 3 and 6 months after the EOT visit.
6. Following progression, new chemotherapy, biochemotherapy, radiation or immunotherapy or any investigational treatment for treatment of the patient's cancer.

AE = adverse event; CT = computerized tomography; CR = complete response; CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; irAE = immune-related AE; mCRPC = metastatic castration-resistant prostate cancer; MEL = melanoma; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PR = partial response; RCC = renal cell carcinoma; SD = stable disease.

Table 17: Pharmacokinetic Sampling Schedule

Study Day	Parts A and A2	Parts B1 and B2[1,7]	Part C[7]	Parts D [redacted]
Cycle 1 Day 1	0 hr pre-dose[2] EOI[3]	0 hr pre-dose[2] EOI[3]	0 hr pre-dose[2] EOI[3]	0 hr pre-dose EOI[3]
Cycle 1 Day 1		0 hr pre-dose[2] (ipi) EOI[3] (ipi)		
Cycle 1 Day 1			0 hr pre-dose[2] (vem) 3 hr post-dose[3,5] (vem)	
Cycle 1 Day 2	EOI + 24.0 hr[4]			
Cycle 1 Day 3	EOI + 48.0 hr[4]			
Cycle 1 Day 8	EOI + 168.0 hr[4]			
Cycle 1 Day 15	0 hr pre-dose[2]		0 hr pre-dose[2] EOI[3]	0 hr pre-dose[2]
Cycle 1 Day 22		0 hr pre-dose[2]		
Cycle 1 Day 29	0 hr pre-dose[2]		0 hr pre-dose[2] EOI[3]	0 hr pre-dose[2]
Cycle 1 Day 29			0 hr pre-dose[2] (vem) 3 hr post-dose[3,5] (vem)	
Cycle 1 Day 43	0 hr pre-dose[2]			
Cycle 2[6] Day 1	0 hr pre-dose[2] EOI[3]		0 hr pre-dose[2] EOI[3]	0 hr pre-dose[2]
Cycle 2[6] Day 29	0 hr pre-dose[2] EOI[3]		0 hr pre-dose[2] EOI[3]	0 hr pre-dose[2] EOI[3]
Cycle 2[6] Day 64		0 hr pre-dose[2] EOI[3]		
Cycle 2[6] Day 64		0 hr pre-dose[2] (ipi) EOI[3] (ipi)		
Cycle 3[6] Day 1	0 hr pre-dose[2]	0 hr pre-dose[2]		
Cycle 4[6] Day 29 and every 4 cycles thereafter	0 hr pre-dose[2]	0 hr pre-dose[2]	0 hr pre-dose[2]	0 hr pre-dose[2]
EOT	At visit	At visit	At visit	At visit
Follow-Up	At visit	At visit	At visit	At visit

1. CX-072 should be administered first, followed by a saline flush, and then the administration of ipilimumab (no sooner than 30 minutes from completion of CX-072 infusion).

2. All pre-dosing samples may be drawn with other study-related blood draws prior to infusion. Vemurafenib predose samples should be collected pre-vemurafenib administration.
3. EOI samples are measured 30 minutes after EOI ± 10 minutes.
4. Sampling windows are as follows: 24 hours ± 6 hours, 48 hours ± 12 hours, 168 hours ± 24 hours.
5. Post-dose samples are measured from the time of the EOI.
6. With the exception of EOI, Cycle 2 and beyond sampling windows are ± 2 days.
7. Sample time point refers to CX-072 unless otherwise specified.

EOI = end of infusion; EOT = end of treatment; hr = hour; ipi = ipilimumab; vem = vemurafenib.

EOI: End of Infusion. All hourly times noted are measured from the end of the infusion.

PK: Serial blood samples will be collected to characterize the single and multidose PK profile of CX-072 when administered alone, and CX-072, ipilimumab, and vemurafenib when administered in combination.

16. ADVERSE EVENTS

16.1. Adverse Event Definitions

16.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

All AEs related to mandated protocol interventions (i.e., screening biopsies) should also be recorded in the eCRF as an AE.

Progressive disease in and of itself, as well as signs and/or symptoms associated with disease progression, is not considered an adverse event or SAE. Progressive disease is an efficacy finding and should not be reported unless the progressive disease results in death during the reporting period. Deaths, reported as SAEs due to progressive disease and considered not related to study drug, will be excluded from treatment-emergent AE analysis.

16.1.2. Suspected Adverse Reaction

A suspected adverse reaction (SAR) is an AE for which there is a reasonable possibility that the study drug(s) caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug(s) and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by the study drug(s).

16.1.3. Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

16.1.4. Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or SAR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE (see definition above),
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

16.1.5. Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or SAR is considered "unexpected":

- If it is not listed in the Reference Safety Information of the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or
- If an Investigator's Brochure is not required or available, the event is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

For marketed products, expectedness assessment for all regions will be performed using the Summary of Product Characteristics per the European Medicines Agency website: www.ema.europa.eu for Yervoy and Zelboraf.

16.2. Adverse Event Classification

16.2.1. Relationship to Investigational Drug

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the IP caused or contributed to an AE. The relationship to IP will be categorized as "Yes" or "No."

16.2.2. Severity

The severity of an event describes the degree of impact upon the patient and/or the need for, and extent of, medical care necessary to treat the event.

Adverse event grading will be defined by the NCI CTCAE v4.03. In the event that the NCI CTCAE v4.03 does not apply, the severity descriptions in Table 18 will be used to describe the maximum intensity of the AE.

Table 18: Adverse Event Severity

Grade	Description
Grade 1	Awareness of sign or symptom, but easily tolerated
Grade 2	Discomfort enough to cause interference with normal daily activities
Grade 3	Inability to perform normal daily activities
Grade 4	Life-threatening consequences; urgent intervention required
Grade 5	Death related to AE

16.3. Exposure in Utero

The patient will be instructed to notify the Investigator if the patient or patient's partner becomes pregnant during the study or within 60 days (105 days for patients enrolled in the UK) after the last dose of study drug. The Investigator must notify the Sponsor within 24 hours via the Pregnancy Notification Form and submit it to the Sponsor. The Investigator should obtain informed consent/assent from the patient or patient's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the patient or patient's partner provides informed consent/assent, the Investigator should follow the pregnancy until outcome. A final Pregnancy Notification Form should be completed when the outcome of the pregnancy is known.

If the outcome of the pregnancy meets criteria for immediate classification as an SAE (e.g. spontaneous abortion, birth defect born to a patient or patient's partner exposed to study drug), the investigator should follow the procedures for reporting an SAE.

16.4. Monitoring of Adverse Event Data

Safety information in the study will be monitored on an ongoing basis by the Medical Monitor and Investigators and discussed at regular teleconferences.

AEs occurring during the reporting period (up to and including 30 days after administration of the last dose of study drug for all adverse events and up to and including 90 days after administration of the last dose of study drug for all immune-related adverse events) should be followed until resolution to baseline status, initiation of a new therapy, or stabilization.

Proper instruction will be provided to each site to ensure prompt reporting and communication between the Sponsor, Investigators, US FDA, and other regulatory agencies regarding any DLTs or other AEs of interest.

For SAEs, the Investigator must record the SAE information in the electronic data capture (EDC) system with as much information as possible and submit it within the time frame described in Section 16.6. When additional information is received (e.g. the outcome of an event is known), the Investigator should record the updated information in the EDC system. If the patient was hospitalized, a copy of the discharge summary and any other relevant hospital records (e.g., admission report, laboratory test results, etc.) should be included as part of the patient's medical file.

All AEs considered to be related (definitely, probably, or possibly related) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved. The type of follow-up (e.g., phone, site visit, etc.) will be left to the discretion of the Investigator.

16.5. Documentation of Adverse Events by Investigator

Patients will be evaluated and questioned generally to identify AEs during the course of the study. Events occurring after the ICF has been signed and prior to administration of the first dose, except AEs related to mandated protocol interventions, will be recorded on the Medical History eCRF. Events occurring after administration of the first dose of study drug and events related to mandated protocol interventions, including those occurring prior to administration of the IP, will be recorded on the AE eCRF. AEs that occur up to and including 30 days after administration of the last dose of study drug and AEs that occur up to and including 90 days after administration of the last dose of study drug for irAEs must be reported in the EDC system.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE eCRF for that visit. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF. In addition, an abnormal test finding will be classified as an AE if 1 or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms;
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy. Note: simply repeating a test, in the absence of any of the other listed criteria, does not constitute an AE;
- The test finding leads to a change in study drug dosing or discontinuation of patient participation in the clinical research study; and/or
- The test finding is considered clinically significant by the Investigator based on his/her medical judgment. If an abnormal laboratory value is recorded as an AE then the corresponding laboratory value must be marked as clinically significant in the database. Similarly, if an abnormal laboratory value is marked as clinically significant in the database it should be recorded as an AE.

When possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this module and the Common Core Document (APPENDIX 1). Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus rather than hyperglycemia).

16.6. Notification About Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

16.6.1. Investigator Reporting to Sponsor

All SAEs that occur after the ICF has been signed must be reported to the Sponsor within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). In addition, all SAEs that occur up to and including 30 days after administration of the last dose of study drug (up to and including 90 days after the last dose of CX-072 for serious irAEs) must be reported to the Sponsor within 24 hours from when the Investigator becomes aware of the SAE. Please refer to Section 16.3 regarding reporting of SAEs associated with pregnancies.

To report the SAE, the Investigator must record the SAE information on the AE eCRF and other relevant eCRFs electronically in the EDC system for the study. When the form is completed, Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to CytomX Safety at safety@cytomx.com, and fax the completed paper SAE form CytomX within 24 hours of awareness. A CytomX eFax number will be provided by Administrative Letter after the filing of Amendment 09. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Investigators must report to the Sponsor any SAE, whether or not considered drug-related, including those listed in the protocol module or Investigator's Brochure. The report must include an assessment of causality.

For all SAEs, the Investigator is obligated to obtain and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a death certificate and summary of available autopsy findings (as applicable) must be submitted as soon as possible to the Sponsor or its designated representative.

16.6.2. Serious Adverse Events Follow-Up

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, the condition stabilizes (in the case of persistent impairment), the patient withdraws consent, the patient is lost to follow-up, the patient dies, or it has been assessed that the study treatment/procedure is not the cause of the AE.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE information electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to CytomX Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

16.6.3. Reporting to Regulatory Agencies and Institutional Review Board/Independent Ethics Committee

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening to the FDA as applicable, applicable competent authorities in all the Member States concerned, and the Central Institutional Review Board (IRB)/Independent Ethics Committee (IEC), as soon as possible, and in any case no later than 7 days after initial knowledge by the Sponsor of such a case, which may include a final SUSAR report 8 days after the initial 7-day notification.

All other SUSARs will be reported to the FDA as applicable, applicable competent authorities in all the Member States concerned, and the Central IRB/IEC as soon as possible, but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required with instructions to submit to local IRB/IECs per local requirements.

16.7. Rapid Notification of Events of Special Interest

In addition to SAEs, the following AESI will be reported to the Sponsor or its designee within 24 hours of site awareness irrespective of seriousness, severity, or causality:

- Any potential Hy's Law case (> 3 × ULN of either ALT/AST with concurrent > 2 × ULN of total bilirubin and lack of alternate etiology)
- Any of the following irAEs defined as: AEs requiring the use of systemic corticosteroids within 30 days after the AE onset date with no clear alternate etiology, or requiring the use of systemic hormonal supplementation:
    - Pneumonitis
    - Colitis
    - Hepatitis (including AST or ALT elevations > 3 × ULN or bilirubin > 1.5 × ULN)
    - Nephritis (including serum creatinine > 1.5 × ULN)
    - Pancreatitis
    - Motor and sensory neuropathy
    - Myocarditis
    - Encephalitis
    - Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, hypophysitis, diabetes mellitus, and adrenal insufficiency)
    - Ocular toxicities (eg, uveitis)
    - Skin reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis, and
    - Diarrhea

Refer to Section 16.6 and the Common Core (APPENDIX 1) for reporting SAEs, DLTs, and AESI.

16.8. Module Specified Events

16.8.1. Module Specified Serious Adverse Events

Grade 3 and 4 AEs and their consequences will not be reported as SAEs in an expedited manner if attributable to underlying disease status or progression.

16.8.2. Module Specified Adverse Events

Patients with advanced cancer enrolling in this study who have received prior treatment may have some degree of bone marrow suppression from prior therapy and/or laboratory abnormalities due to underlying disease status. Only changes in the grade of baseline laboratory values that require intervention (e.g., transfusions, delay in study drug administration) should be reported as AEs.

Progression of disease (including the major signs and symptoms of disease progression) is a study endpoint and should not be reported as an AE/SAE. However, when a patient dies from any cause, including disease progression, the death should be reported as an SAE.

CX-072

There have been no clinical studies conducted to date with CX-072. Reported serious events of special interest with other PD-1/PD-L1 agents include irAEs of pneumonitis; colitis; hepatitis; and endocrinopathies of the thyroid, adrenal gland, and pituitary gland. Reported immune-related adverse reactions with other PD-1/PD-L1 agents include meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels. Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection have been reported. In addition, Grade 3 and 4 infusion reactions requiring discontinuation of study drug have also been reported.

Refer to the Investigator's Brochure for a summary of nonclinical toxicology information.

Ipilimumab

- Refer to the current package insert for ipilimumab (Yervoy US Package Insert, 2015) for common adverse reactions, black box warnings, and other information pertaining to the management of AEs associated with ipilimumab treatment.
- Most common adverse reactions (≥ 5%) are fatigue, diarrhea, pruritus, rash, and colitis.

BLACK BOX WARNING: Can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.

Permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries, including liver function tests and thyroid function tests at baseline and before each dose.

Vemurafenib

- **Most common adverse reactions** (≥ 30%) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma.
- **New primary malignancies:**
  - cSCC, keratoacanthoma, and melanoma were observed at a higher incidence in patients receiving vemurafenib compared with patients in the control arm. Dermatologic evaluations prior to initiation of therapy and every 2 months while on therapy should be performed. Dermatologic monitoring for 6 months following discontinuation of vemurafenib should be considered.
- **Hypersensitivity reactions:** Anaphylaxis and other serious hypersensitivity reactions during treatment and re-initiation of treatment (generalized rash and erythema, hypotension, and drug reaction with eosinophilia and systemic symptoms [DRESS syndrome]). Permanently discontinue vemurafenib in patients who experience a severe hypersensitivity reaction.
- **Dermatologic reactions:** Permanently discontinue vemurafenib in patients who experience a severe dermatologic reaction (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis).
- **QT prolongation:** Do not start treatment in patients with uncorrectable electrolyte abnormalities, QTc ≥ 500 ms, or long QT syndrome, or in patients who are taking medicinal products known to prolong the QT interval. Prior to and following treatment initiation or after dose modification for QTc prolongation, evaluate ECG and electrolytes (including potassium, magnesium, and calcium) after 15 days, monthly during the first 3 months, and then every 3 months thereafter or more often as clinically indicated. See other recommendations in prescribing information (Zelboraf US Package Insert, 2017).
- **Hepatotoxicity:** Liver injury leading to functional hepatic impairment, including coagulopathy or other organ dysfunction – monitor transaminases, alkaline phosphatase, and bilirubin before initiation of treatment and monthly during treatment, or as clinically indicated. Manage laboratory abnormalities with dose reduction, treatment interruption, or treatment discontinuation.

- **Photosensitivity:** Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum ultraviolet A/ultraviolet B sunscreen and lip balm (sun protection factor ≥ 30) when outdoors.
- **Ophthalmologic reactions:** Uveitis, blurry vision, and photophobia can occur in patients treated with vemurafenib.
- **Radiation sensitization and radiation recall:** These effects are possible in patients treated with radiation prior to, during, or subsequent to vemurafenib treatment.

16.9. Emergency Identification of Study Medication

Study CTMX-M-072-001 is open label. Emergency identification of study medication does not apply.

17. ETHICS

17.1. Institutional Review Board or Independent Ethics Committee

The IRB/IEC will meet all FDA requirements governing IRBs (21 CFR Part 56).

The Investigator will provide the Sponsor (or designee) with documentation of IRB/IEC approval of the following documents before the study begins at the study site(s): protocol, ICF, and any other relevant materials intended for or directed to patients (e.g., patient diaries, advertisements). The Investigator will supply documentation to the Sponsor of IRB/IEC requirements regarding continuing review and approval of revisions to any of these documents.

17.2. Ethical Conduct of the Study

This study will be conducted in accordance with the current IRB/IEC approved clinical protocol, International Conference on Harmonisation Good Clinical Practice Guidelines, and relevant policies and requirements of the national regulations and laws, including the Health Insurance Portability and Accountability Act of 1996.

17.3. Patient Information and Informed Consent

Written informed consent/assent is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Patients regulations listed in 21 CFR Part 50.

The ICF will be used to explain the risks and benefits of study participation in simple terms before the patient will be entered into the study. The ICF will contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Written informed consent must be given by the patient after the receipt of detailed information on the study. It is the responsibility of the Investigator to obtain consent/assent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by the Sponsor or its designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor.

18. STUDY ADMINISTRATION

18.1. Common Core Document Amendments

Changes to the conduct of the study should be prepared as an amendment to the Common Core Document or a module amendment and implemented only upon approval of the Sponsor or a representative of the Sponsor. Protocol amendments should also receive written IRB/IEC approval and, where appropriate, Competent Regulatory Authority approval prior to implementation, except when necessary to eliminate immediate hazards to the patients or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB/IEC, as appropriate.

18.2. Module Amendments

Changes to the conduct of the study will be prepared by the Sponsor as an amendment to the Module and/or the Clinical Core Protocol and implemented only upon joint approval of the Sponsor, or a representative of the Sponsor, and the Investigator(s). Amendments should also receive written IRB/IEC approval and, where appropriate, Competent Regulatory Authority approval prior to implementation, except when necessary to eliminate immediate hazards to the patients or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB/IEC, as appropriate.

19. LONG-TERM EXTENSION INTRODUCTION

19.1. Long-term Extension Rationale

Study CTMX-M-072-001 as described in Section 4 through Section 18 was the first clinical study under which CX-072 was studied in humans. The long-term extension part of Study CTMX-M-072-001 as described in Section 19 through Section 27 is an extension of the study for patients previously enrolled in the parent study CTMX-M-072-001 who remain active on CX-072 treatment and wish to continue therapy with CX-072. Patients who are receiving study treatment with CX-072 monotherapy, and who continue to derive clinical benefit without unacceptable toxicity as determined by the Investigator, will be eligible to enroll in the long-term extension. Patients will be provided CX-072 treatment for a maximum of 12 months as calculated from the initiation of treatment in the long-term extension and will be followed to assess long-term safety of CX-072.

20. LONG-TERM EXTENSION OBJECTIVE

20.1. Primary Objective

The primary objective of the long-term extension is to maintain CX-072 treatment for patients experiencing ongoing clinical benefit and to assess long-term safety of CX-072 monotherapy.

20.2. Long-term Extension Study Design

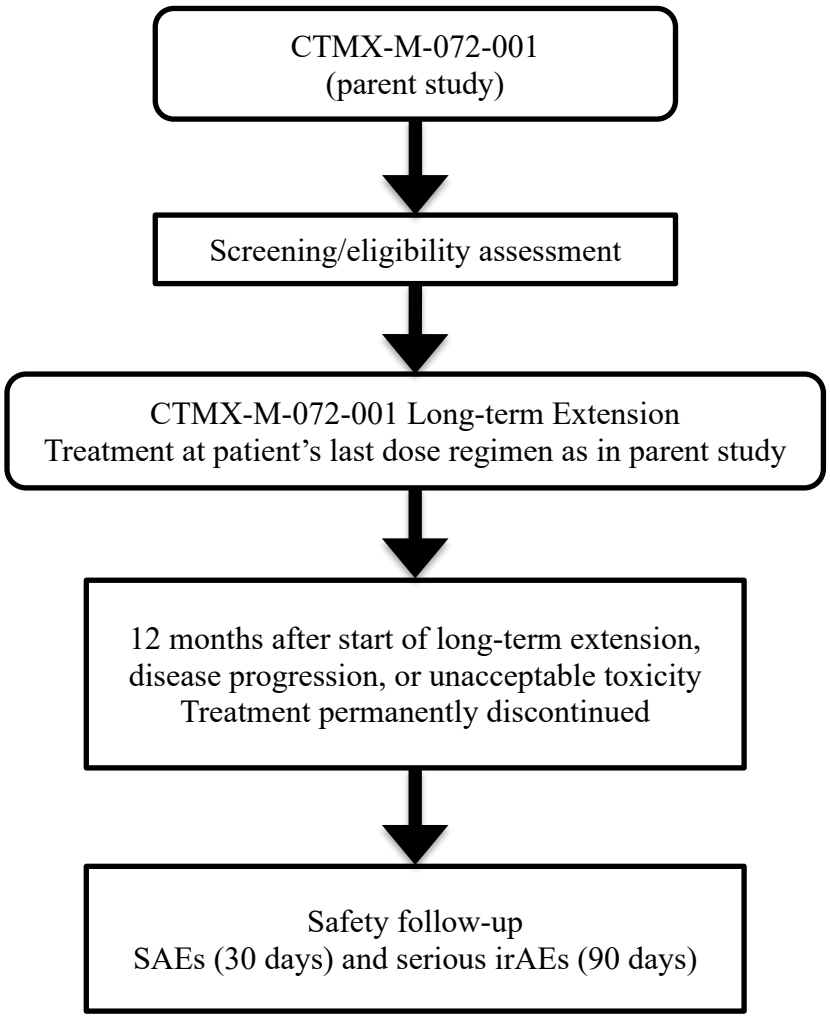
The long-term extension provides continued access to CX-072 monotherapy and evaluates the long-term safety of CX-072 in patients with solid tumor malignancies who have previously participated in the parent study CTMX-M-072-001.

Patients from Study CTMX-M-072-001 are eligible to enroll in the long-term extension if they are actively receiving CX-072 monotherapy and will continue to benefit from treatment with CX-072 monotherapy as determined by the Investigator.

Eligible patients must sign a new informed consent for this study.

For the long-term extension, a CX-072 monotherapy treatment cycle will consist of 14 days.

Figure 9: Long-Term Extension Study Schema



21. LONG-TERM EXTENSION STUDY ELIGIBILITY CRITERIA

21.1. Inclusion Criteria

1. Previously enrolled in Study CTMX-M-072-001 Parts A-E for at least 12 months (as calculated from the patient's prior Cycle 1, Day 1 to the first infusion administered in the long-term extension
2. Actively receiving CX-072 monotherapy; patients must be assessed by the Investigator as still receiving clinical benefit from CX-072 in Study CTMX-M-072-001 without unacceptable toxicity
3. Demonstrated compliance as assessed by the Investigator during Study CTMX-M-072-001
4. Women of childbearing potential and males must agree to use a highly effective method of contraception (details provided in APPENDIX 5) prior to study entry, while taking study drug, and for a period of 105 days following the last treatment
5. Written informed consent must be obtained prior to enrolling in the long-term extension

21.2. Exclusion Criteria

1. Illness or medical condition which in the opinion of the investigator could compromise the patient's safety at enrollment
2. Prohibited concomitant therapy outlined in the protocol
3. Concurrent participation in another therapeutic clinical trial

22. LONG-TERM EXTENSION ENROLLMENT AND STUDY PROCEDURES

22.1. Informed Consent

Patients must sign a new informed consent form for the long-term extension before receiving the first dose of CX-072 under Protocol Amendment 09.

22.2. Enrollment

Patients will be enrolled using an interactive web response system (IWRS). The investigative site will log into the IWRS to enroll a patient who meets eligibility criteria for the long-term extension. Each patient enrolled in the long-term extension will receive a unique patient number upon enrollment. Individual patient data from the parent study and this current long-term extension will be linked by another unique identifier. An individual patient will have the same unique identifier across both study parts (parent study and long-term extension). Once assigned, numbers will not be re-used. Study treatment must commence within 7 days after enrollment but not earlier than 14 days from previous dose received in parent CTMX-072-001 study. At each medical center, patients must be approached for informed consent to enter the long-term extension at their next clinic visit following the approval of Protocol Amendment 09.

22.3. CX-072 Dispensation

CX-072 will be dispensed by the study site personnel to patients at scheduled study visits.

22.4. Safety Assessment

Safety assessments will be performed at all visits to the site throughout study treatment per disease-specific standard of care.

Assessments such as physical examination, vital signs, and patient weight will be performed at each study visit per standard of care. Significant signs and symptoms will be monitored throughout the study. Electrocardiogram should be performed if clinically necessary.

22.5. Tumor Imaging

Assessment for tumor response and disease progression should be conducted according to standard of care, including the frequency and modality of imaging. The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed upon by the Sponsor Medical Monitor and documented in the study records.

22.6. Laboratory Assessments

Laboratory assessments should be performed per standard of care for anti-PD-1/PD-L1 therapy, including complete blood counts with differential, chemistry panel, thyroid function tests, and pregnancy tests.

For the long-term extension, PK, ADA, and exploratory blood sampling will be discontinued.

22.7. End of Treatment

The reason and date for discontinuation from treatment will be recorded on the eCRF.

Table 19: Schedule of Events for Long-term Extension

Period/Procedure	Treatment Period		
	Screening Period	**Cycles 1 - n** ± 2 days of scheduled visit	**EOT[9]**
Study/Visit Day[1]	**-7 to 0**	**Day 1**	
Informed Consent and confirmation of participation in prior protocol	X		
AE Assessment[2]		X	X
Study Drug Administration			
CX-072 Infusion[3]		X	
Imaging			
CT/MRI [4]		Per institution standard of care	
Laboratory Assessments			
Hematology[5]		Per institution standard of care	
Serum Chemistry[6]		Per institution standard of care	
Thyroid Function[7]		Per institution standard of care	
Pregnancy Test[8]	Per institution standard of care	Per institution standard of care	

Note: A treatment cycle consists of 14 days. AE = adverse event; CT = computed tomography; MRI = magnetic resonance imaging; T4 = thyroxine; TSH = thyroid-stimulating hormone.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity should be completed as close to the scheduled date as possible.
2. All AEs will be assessed and reviewed prior to infusion during study visit. SAEs are to be reported up to and including 30 days after the last dose of CX-072 and up to and including 90 days after last dose of CX-072 for serious irAEs.
3. Patients shall continue the same dose of CX-072 that they last received in the previous cohort (Parts A-E) of the study that they were enrolled in. No dose increase or decrease of CX-072 is permitted in long-term extension.
4. CT and/or MRI should be repeated per institutional standard of care.
5. CBC with differential for long-term extension should be performed at the frequency per institution standard of care for anti-PD-1/PD-L1 therapy.
6. Chemistry testing for long-term extension should be performed per institution standard of care for anti-PD-1/PD-L1 therapy.
7. TSH and free T4 for long-term extension should be performed at the frequency per institution standard of care for anti-PD-1/PD-L1 therapy.
8. Urine pregnancy test (with serum test as needed for confirmation) should be obtained for long-term extension at the frequency per institution standard of care for anti-PD-1/PD-L1 therapy. Pregnancies in the patient or patient's partner within 60 days (105 days in the UK) after the last dose are to be reported to the Sponsor within 24 hours via the Pregnancy Notification Form.
9. An EOT visit will be conducted at the conclusion of treatment or within 7 days of the last dose. Once a patient has met a withdrawal criterion for study drug treatment, participation in this study will only occur for safety purposes. Survival follow-up will no longer occur.

22.8. Follow-Up Phase

The follow-up phase will only comprise safety follow-up for 30 days after the last dose of study drug to report SAEs and 90 days for serious irAEs that may have occurred after the patient discontinued study treatment. All SAEs including serious irAEs will be followed until resolution or until the Investigator declares the toxicity is stable. Survival information will not be collected following the last dose of study drug.

23. LONG-TERM EXTENSION STUDY TREATMENT

See Section 11 for CX-072 packaging, labeling, handling, storage, accountability, and disposal information.

Dosage and Administration

For the long-term extension, a patient may receive up to 12 months of therapy, calculated from the first infusion date administered under Protocol Amendment 09. This length of time was determined with the understanding that all patients enrolled into this extension protocol would have had the opportunity to receive a minimum of 2 years in total of treatment with this investigational agent.

In the long-term extension, the dose and schedule of CX-072 will be the same as the last administered dose and schedule in the parent study CTMX-M-072-001. For example, if the patient was last treated with CX-072 10 mg/kg in the parent study cohort, then the dose of CX-072 will continue at 10 mg/kg every 2 weeks in the long-term extension. The dose of CX-072 shall not be increased or decreased at the time of enrollment in the long-term extension.

23.1. Dose Interruption and Modification

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. There must be a minimum of 14 days between study drug infusions. Therapy with CX-072 in the long-term extension may continue for up to 12 months year for each patient, with the rationale previously stated above in Section 19.1.

In the long-term extension, an infusion may be delayed for up to 14 days. A patient must discontinue study drug if he/she cannot safely receive an infusion of CX-072 for 84 days, calculated from the last treatment date. If a patient is receiving corticosteroids on a taper, the daily dose of prednisone must be < 10 mg/day (or its equivalent) for an infusion to be administered.

23.2. Management of Infusion Reactions

See Section 11.6 for management of infusion reactions.

24. DSMB MONITORING

There will be no DSMB monitoring in the long-term extension study.

25. LONG-TERM EXTENSION STUDY

25.1.1. Prior Therapy

Patient's prior therapy captured in the parent study CTMX-M-072-001 will not be collected again in the long-term extension.

25.1.2. Prohibited Medications

Patients should not receive other anticancer therapy (cytotoxic, biologic, or hormone other than for replacement), live vaccines, or experimental therapy while on treatment in this study. The use of herbal medication should be discouraged per standard of care.

26. LONG-TERM EXTENSION STUDY SAFETY MONITORING AND REPORTING

See Section 16 for AE definitions, classification, exposure in utero, monitoring, and documentation.

26.1. Adverse Event Reporting for the Long-Term Extension

All AEs including possible cases of Hy's Law or immune-related AEs (as described in Section 16.7) will be collected in the long-term extension. SAEs are reportable through 30 days after the last dose of study drug and through 90 days after administration of the last dose of study drug for serious irAEs (see Section 16.6 and Section 16.7).

27. LONG-TERM EXTENSION STATISTICAL CONSIDERATIONS

Details of the statistical analyses will be included in a separate long-term extension Statistical Analysis Plan (SAP).

28. REFERENCES

P450 Drug Interaction Table. Indiana University: Department of Medicine; 2015. Cited 2016 Aug 01. Available from: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, et al. Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): Preliminary data from KEYNOTE-086 cohort B. J Clin Oncol 35, 2017 (suppl; abstr 1088).

Adams S, Schmid P, Rugo HS, Winer EP, Loirat D, et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. J Clin Oncol 35, 2017 (suppl; abstr 1008).

Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, et al. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010 Jan;37(1):20-7. PubMed PMID: 19638070.

Arparicio T, Zaanan A, Svrcek M, Laurent-Puig P, Carrere N, et al. Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. Dig Liver Dis. 2014 Feb;46(2):97-104. PubMed PMID: 23796552.

Bhatia S, Afanasiev O, Nghiem P. Immunobiology of Merkel cell carcinoma: implications for immunotherapy of a polyomavirus-associated cancer. Curr Oncol Rep. 2011 Dec;13(6):488-97. PubMed PMID: 21953511.

Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, et al. Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65. PubMed PMID: 22658128.

Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41. doi:10.2307/2530286.

Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J Surg Oncol. 2012 Dec;106(7):811-5. PubMed PMID: 22592943.

Burgess MA, Bolejack V, Van Tine BA, Schuetze S, Hu J, et al. Multicenter phase II study of pembrolizumab in advanced soft tissue and bone sarcomas: final results of SARC028 and biomarker analyses. J Clin Oncol 35, 2017 (suppl; abstr 11008).

Cardoso F, Costa A, Norton L, Senkus E, Aapro M, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast. 2014 Oct;23(5):489-502. PubMed PMID: 25244983.

Cho J, Ahn M, Yoo KH, Lee H, Kim HK, et al. A phase II study of pembrolizumab for patients with previously treated advanced thymic epithelial tumor. J Clin Oncol 35, 2017 (suppl; abstr 8521).

Cooper ZA, Juneja VR, Sage PT, Frederick DT, Piris A, et al. Response to BRAF inhibition in melanoma is enhanced when combined with immune checkpoint blockade. Cancer Immunol Res. 2014 Jul;2(7):643-54. PubMed PMID: 24903021.

Curigliano G, Goldhirsch A. The triple-negative subtype: new ideas for the poorest prognosis breast cancer. J Natl Cancer Inst Monogr. 2011;2011(43):108-10. PubMed PMID: 22043054.

Cytel. EAST®. Version 6.4.1. https://www.cytel.com/software/east#section_east. Accessed 16 October 2018.

Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004 Aug1;101(3):518-26. PubMed PMID: 15274064.

Deng R, Bumbaca D, Pastuskovas CV, Boswell CA, West D, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs. 2016;8(3):593-603. PubMed PMID: 26918260.

Dietze EC, Sistrunk C, Miranda-Carboni G, O'Regan R, Seewaldt VL. Triple-negative breast cancer in African-American women: disparities versus biology. Nat Rev Cancer. 2015 Apr;15(4):248-54. PubMed PMID: 25673085.

Dirix LY, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, et al. Avelumab, an anti–PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2018 Feb;167(3):671-686. PubMed PMID: 29063313.

Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010 Oct;5(10 Suppl 4):S260-5. PubMed PMID: 20859116.

FDA BLA 761049: Multidisciplinary Review and Evaluation. Version date: 01 February 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000TOC.cfm. Accessed 22 March 2018.

Foote MC, McGrath M, Guminski A, Hughes BG, Meakin J, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann Oncol. 2014 Oct;25(10):2047-52. PubMed PMID: 25091317.

Frazier KS, Engelhardt JA, Fant P, Guionaud S, Henry SP, et al. Scientific and Regulatory Policy Committee Points-to-consider Paper*: Drug-induced Vascular Injury Associated with Nonsmall Molecule Therapeutics in Preclinical Development: Part I. Biotherapeutics. Toxicol Pathol. 2015 Oct;43(7):915-34. PubMed PMID: 25722122.

Gandara DR, Kowanetz M, Mok T, Rittmeyer A, Fehrenbacher L, et al. Blood-based biomarkers for cancer immunotherapy: Tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L+ NSCLC (POPLAR and OAK). Presented at: 2017 ESMO Congress; Madrid, Spain; September 9-12, 2017. Abstract 1295O.

Giaccone G, Thompson J, McGuire C, Manning M, Kallakury B, et al. Pembrolizumab in patients with recurrent thymic carcinoma: results of a phase II study. J Clin Oncol 35, 2017 (suppl; abstr 8573).

Giaccone G, Kim C, Thompson J, McGuire C, Kallakury B, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol. 2018 Jan 25. Epub ahead of print. PubMed PMID: 29395863.

Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A. Radiation therapy definitions and reporting guidelines for thymic malignancies. J Thorac Oncol. 2011 Jul;6(7 Suppl 3):S1743-8. PubMed PMID: 21847057.

Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton JK, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res. 2011 Mar 1;17(5):1082-9. PubMed PMID: 21233401.

Gucalp A, Traina TA. Triple-negative breast cancer: adjuvant therapeutic options. Chemother Res Pract. 2011;2011:696208. PubMed PMID: 22312556.

Hamid O, et al. Preliminary clinical safety, tolerability and activity of atezolizumab (anti–PD-L1) combined with Zelboraf in BRAFv600 metastatic melanoma. Society for Melanoma Research 2015 International Congress; 2015 Nov 18-21.

Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, et al. Predictive correlates of response to the anti–PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528):563-7. PubMed PMID: 25428504.

Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol. 2005 Jan;89(1):1-4. PubMed PMID: 15611998.

Jamdade VS, Sethi N, Mundhe NA, Kumar P, Lahkar M, et al. Therapeutic targets of triple-negative breast cancer: a review. Br J Pharmacol. 2015 Sep;172(17):4228-37. PubMed PMID: 26040571.

Johnson DB, Wallender EK, Cohen DN, Likhari SS, Zwerner JP, et al. Severe cutaneous and neurologic toxicity in melanoma patients during vemurafenib administration following anti–PD-1 therapy. Cancer Immunol Res. 2013 Dec;1(6):373-7. PubMed PMID: 24490176.

Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. 2016 Nov 3;375(18):1749-55. PubMed PMID: 27806233.

Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013 Jun;68(6):957-66. PubMed PMID: 23375456.

Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016 Oct;17(10):1374-1385. PubMed PMID: 27592805.

Kim JR, Moon YJ, Kwon KS, Bae JS, Wagle S, et al. Tumor infiltrating PD-1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. PLoS One. 2013 Dec 11;8(12):e82870.

Koga K, Matsuno Y, Noguchi M, Mukai K, Asamura H, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int. 1994 May;44(5):359-367. PubMed PMID: 8044305.

Koyama T and Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008 Jul 20;27(16):3145-3154. PubMed PMID: 17960777.

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23-34. PubMed PMID: 26027431.

LeBeau AM, Lee M, Murphy ST, Hann BC, Warren RS, et al. Imaging a functional tumorigenic biomarker in the transformed epithelium. Proc Natl Acad Sci U S A. 2013 Jan 2;110(1):93-8. PubMed PMID: 23248318.

Linch M, Miah AB, Thway K, Judson IR, Benson C. Systemic treatment of soft-tissue sarcoma-gold standard and novel therapies. Nat Rev Clin Oncol. 2014 Apr;11(4):187-202.

Lipson EJ, Forde PM, Hammers HJ, Emens LA, Taube JM, et al. Antagonists of PD-1 and PD-L1 in Cancer Treatment. Semin Oncol. 2015 Aug;42(4):587-600. PubMed PMID: 26320063; NIHMSID: NIHMS699153.

Lipson EJ, Vincent JG, Lovo M, Kagohara LT, Luber BS, et al. PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. Cancer Immunol Res. 2013 Jul;1(1):54-63. PubMed PMID: 24416729.

Mantripragada K and Birnbaum A. Response to Anti–PD-1 Therapy in Metastatic Merkel Cell Carcinoma Metastatic to the Heart and Pancreas. Cureus. 2015 Dec 13;7(12)e403. PubMed PMID: 26824006.

Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011 Sep 1;29(25):3149-26. PubMed PMID: 21810686.

Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017 Apr;18(4):446-453. PubMed PMID: 28223062.

Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol. 2016 Jul 30;34(21):2460-7. PubMed PMID: 27138582.

NCCN Clinical Practice Guidelines in Oncology Squamous Cell Skin Cancer. Version 2.2018; 2017 October 05.

NCCN Clinical Practice Guidelines in Oncology Thymomas and Thymic Carcinomas. Version 1; 2018 Jan 25.

Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev. 1998 Mar;7(3):243-51. PubMed PMID: 9521441.

Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med. 2016 Jun 30;374(26):2542-52. PubMed PMID: 27093365.

Ogawa K, Toita T, Uno T, Fuwa N, Kakinohana Y, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. Cancer. 2002 Jun 15;94(12):3115-9. PubMed PMID: 12115342.

Ott PA, Piha-Paul SA, Munster P, Pishvaian MJ, van Brummelen EMJ, et al. Safety and antitumor activity of the anti–PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol. 2017 May 1;28(5):1036-41. PubMed PMID: 28453692.

Overall CM, Kleifeld O. Tumour microenvironment - opinion: validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy. Nat Rev Cancer. 2006 Mar;6(3):227-39. PubMed PMID: 16498445.

Overman MJ, Varadhachary GR, Kopetz S, Adinin R, Lin E, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol. 2009 Jun 1;27(16):2598-603. PubMed PMID: 19164203.

Papadopoulos KP, Owonikoko TK, Johnson M, Brana I, Martin MG, et al. Cemiplimab (REGN2810): A fully human anti–PD-1 monoclonal antibody for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC)—Initial safety and efficacy from expansion cohorts (ECs) of phase I study. J Clin Oncol 36, 2018 (suppl 5S; abstr 195).

Pedersen K, Smyrk TC, Harrington S, McWilliams RR. Programmed death-ligand 1 (PD-L1) expression in small bowel adenocarcinomas (SBA). J Clin Oncol 33, 2015 (suppl; abstr 3618).

Penault-Llorca F, Viale G. Pathological and molecular diagnosis of triple-negative breast cancer: a clinical perspective. Ann Oncol. 2012 Aug;23 Suppl6:vi19-22. PubMed PMID: 23012297.

Pollack SM, He Q, Yearley JH, Emerson R, Vignali M, et al. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas. Cancer. 2017 May 2. Epub ahead of print. PubMed PMID: 28463396.

Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, et al. MPDL3280A (anti–PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014 Nov 27;515(7528):558-62. PubMed PMID: 25428503.

Riaz N, Havel JJ, Makarov V, Desrichard A, Urba WJ, et al. Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. Cell. 2017 Nov 2:171(4):934-949.e15. PubMed PMID: 29033130.

Rizvi N, Gettinger S, Goldman J, Hellmann M, Chow L, et al. Safety and efficacy of first-line nivolumab (anti–programmed death-1 [PD-1]) and ipilimumab in non-small cell lung cancer (NSCLC). World Conference on Lung Cancer; 2015 Sep 6-9.

Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single arm, phase 2 trial. Lancet. 2016 May 07;387(10031):1909-20. PubMed PMID: 26952546.

Safieddine N, Liu G, Cuningham K, Ming T, Hwang D, et al. Prognostic factors for cure, recurrence and long-term survival after surgical resection of thymoma. J Thorac Oncol. 2014 Jul;9(7):1018-22. PubMed PMID: 24926546.

Segal NH, Ou S-H I, Balmanoukian AS, Fury MG, Massarelli E, et al. Safety and efficacy of MEDI4736, an anti–PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 33, 2015 (suppl; abstr 3011).

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan;68(1):7-30. PubMed PMID: 29313949.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989 Mar;10(1):1-10. PubMed PMID: 2702835.

Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014 Dec 4;371(23):2189-2199. PubMed PMID: 25409260.

Spigel DR, Reckamp KL, Rizvi NA, Poddubskaya E, West HJ, et al. Clinical activity and safety from a Phase II study (FIR) of atezolizumab (anti-PDL1) in PD-L1–selected patients with non-small cell lung cancer (NSCLC). J Clin Oncol 33, 2015 (suppl; abstr 8009).

Stroh M, Winter H, Marchand M, Claret L, Eppler S, et al. Clinical pharmacokinetics and pharmacodynamics of atezolizumab in metastatic urothelial carcinoma. Clin Pharmacol Ther. 2017 Aug;102(2):305-312. PubMed PMID: 27981577.

Tai PT, Yu E, Winquist E, Hammond A, Stitt L, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. J Clin Oncol. 2000 Jun;18(12):2493-9. PubMed PMID: 10856110.

Thota R, Gonzalez RS, Berlin J, Cardin DB, Shi C. Could the PD-1 Pathway Be a Potential Target for Treating Small Intestinal Adenocarcinoma? Am J Clin Pathol. 2017 Sep 1;148(3):208-214. PubMed PMID: 28821192.

Tilston P. Anal human papillomavirus and anal cancer. J Clin Pathol. 1997 Aug;50(8):625-34. PubMed PMID: 9301544.

William WN Jr, Feng L, Ferrarotto R, Ginsberg L, Kies M, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: A single-arm phase II clinical trial. J Am Acad Dermatol. 2017 Dec;77(6):1110-3. PubMed PMID: 28964539.

Xiang XJ, Liu YW, Zhang L, Qiu F, Yu F, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anticancer Drugs. 2012 Jun;23(5):561-6. PubMed PMID: 22481063.

Yang HK, Jeong KC, Kim YK, Jung ST. Role of matrix metalloproteinase (MMP) 2 and MMP-9 in soft tissue sarcoma. Clin Orthop Surg. 2014 Dec;6(4):443-54. PubMed PMID: 25436070.

Yervoy® US Package Insert. Rev 10/2015. Approval 03/2011.

Zelboraf® US Package Insert. Rev 05/2016. Approval 08/2011.

29. APPENDICES

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APPENDIX 2. THYMIC EPITHELIAL TUMOR CLASSIFICATION AND STAGING

2015 World Health Organization Classification of Thymic Epithelial Tumors

Tumor Type	Tumor Characteristics
Thymoma Type A	Occurrence of bland, spindle shaped epithelial cells (at least focally); paucity[1] of absence of immature (TdT+) T-cells throughout the tumor.
Thymoma Type A/B	Occurrence of bland, spindle shaped epithelial cells (at least focally); abundance of immature (TdT+) T-cells focally or throughout tumor.
Thymoma Type B1	Thymus-like architecture and cytology; abundance of immature T-cells; area of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelia cells without clustering (e.g., < 3 contiguous epithelial cells).
Thymoma Type B2	Increased number of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T-cells.
Thymoma Type B3	Sheets of polygonal slightly moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T-cells.
Thymic Carcinoma	Lacks immature T-cell lymphocytes present in thymomas.

1. Paucity versus abundance: any area of crowded immature T-cells or moderate number of immature T-cells in > 10% of the investigated tumor are indicative of "abundance."

TdT+ = terminal deoxynucleotidyl transferase positive.

Adapted from Marx A, Chan JK, Coindre JM, Detterbeck F, Girard N, et al. The 2015 World Health Organization classification of tumors of the thymus: continuity and changes. J Thorac Oncol. 2015 Oct;10(10):1383-1395. PubMed PMID: 26295375.

Masaoka-Koga Staging of Advanced Thymic Epithelial Tumors

Stage	Criteria
II	Microscopic transcapsular invasion or macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium.
III	Macroscopic invasion of neighboring organs (i.e., pericardium, great vessel, or lung).
IVA	Pleural or pericardial dissemination.
IVB	Lymphatic or hematogenous dissemination.

Koga K, Matsuno Y, Noguchi M, Mukai K, Asamura H, et al. A review of 79 thymomas: Modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int. 1994 May;44(5):359-367. PubMed PMID: 8044305.

APPENDIX 3. DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) has been established for the study. The DSMB will consist of individuals with pertinent expertise in clinical trials in oncology, immunology, and statistics who will review, on a regular basis, accumulating safety data from this ongoing study. The DSMB will also be notified of protocol amendments. The DSMB will be charged with responsibility to advise CytomX with regard to:

1. The continuing safety of current and future participants in the study, and
2. The continuing validity and scientific merit of the study.

For Parts A[redacted] of this study, the DSMB will convene at least 2 times per year in accordance with meetings scheduled to review the overall CX-072 program; more frequent meetings will be dictated by the availability and severity of ongoing safety information. Meetings will be held with the appointed representatives of the Statistical and Medical Groups from CytomX. The DSMB will review all available information to determine whether the study will continue unchanged or whether protocol modifications are required to ensure patient safety. Recommendations for closing should be on the basis of excessive toxicity in the statistics report or the aggregated safety data or lack of efficacy. This determination will be documented by a letter from the DSMB. In the event that the DSMB advises a major change in the study design or conduct, such as early termination, this advice will be transmitted to the Sponsor.

The DSMB will consist of at least 3 members. DSMB member(s) who withdraw prior to completion of the project will be replaced. Should it become necessary to expand the number of DSMB members, CytomX will appoint additional members. Upon first site activation of Protocol Amendment 09 (with the transition to long-term extension), the responsibilities of the DSMB for this trial will end.

APPENDIX 4. SAFETY REVIEW COMMITTEE

For Parts A-E of this study, a Safety Review Committee (SRC) has been established for the study. The SRC will consist of selected Investigators from the trial and representatives from CytomX who will review on a regular basis, approximately monthly, the cumulative safety data from each cohort in the study in order to:

1. Approve dose escalation to the next cohort in each part of the study;
2. Recommend modifications to the dose or schedule as it pertains to patient safety;
3. Recommend modifications to the protocol related to patient oversight (e.g., additional safety monitoring, changes to inclusion/exclusion criteria); or
4. Evaluate combination schedules to recommend modifications to the combination dosing schedule/regimen.

Actions taken regarding dose escalation or amendments to the protocol will be documented and stored in the trial master file for the study. An SRC will not be convened for the long-term extension.

APPENDIX 5. CONTRACEPTION GUIDELINES

The Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation;
  - Oral, intravaginal, or transdermal;
- Progestogen-only hormonal contraception associated with the inhibition of ovulation;
  - Oral, injectable, or implantable;
- An intrauterine device;
- Intrauterine hormone-releasing system;
- Bilateral tubal occlusion;
- Vasectomized partner; and
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and if used, this method must be used in combination with another acceptable method listed above.

Definition of childbearing potential:

Childbearing potential is defined as being physiologically capable of becoming pregnant. No childbearing potential is defined as one or both of the following criteria:

- Surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy); and/or
- Post-menopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months, OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a post-menopausal follicle-stimulating concentration > 30 IU/mL.

Source: Clinical Trial Facilitation Group (CTFG) (2014). Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/

01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed June 22, 2018.